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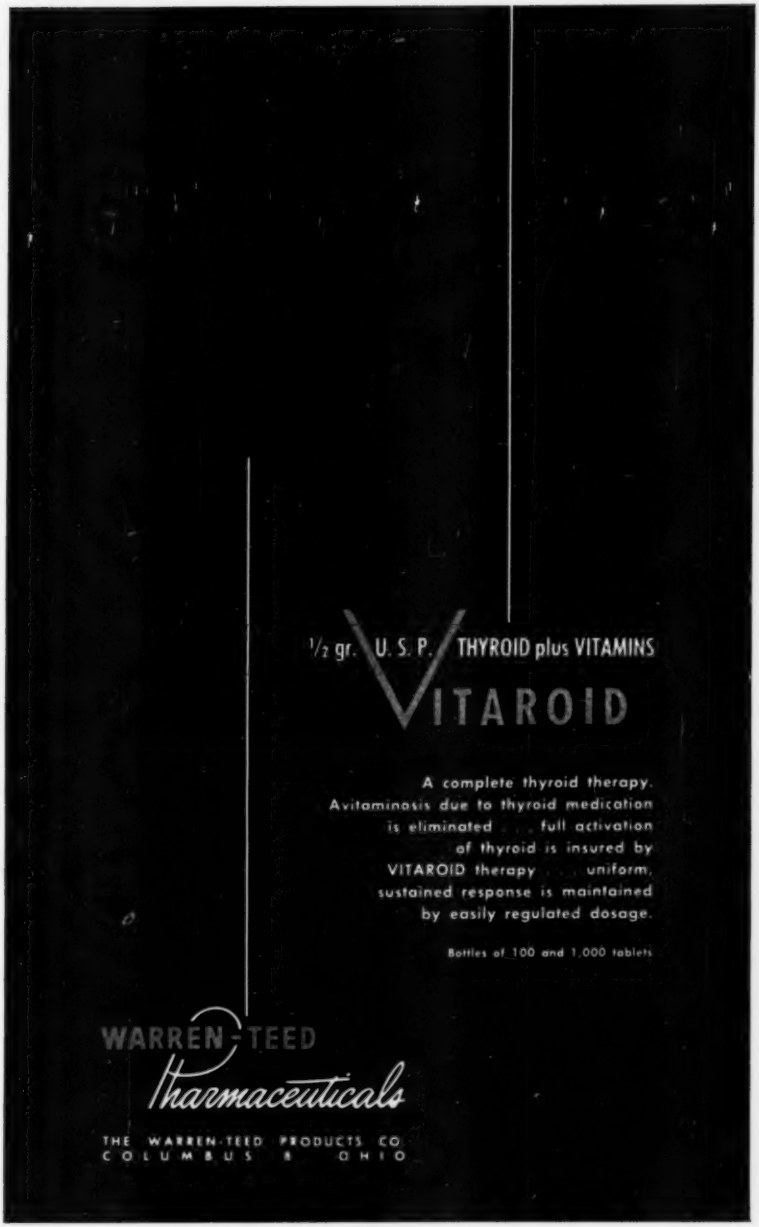
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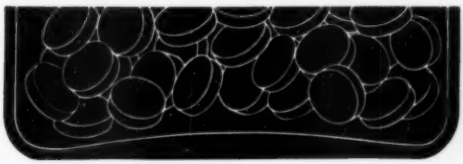

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1. Morrison, L. M. and Johnson, K. D.: Amer. Heart J. 39:31, Jan. 1950.
2. Herrmann, G. R.: Exp. Med. & Surg. 5:149, May-Aug. 1947.
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BULLETIN OF
THE NEW YORK ACADEMY
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VOL. 26, NO. 10 OCTOBER 1950

THE CLINICAL USE OF RADIOACTIVE ISOTOPES*

The Ludwig Kast Lecture

JOHN HUNDALE LAWRENCE

Director, Donner Laboratory of Medical Physics, University of California, Berkeley**

THE study of radioactivity began in 1896 when the radioactivity of uranium was discovered. From that time until 1932 the only radioactive elements were those which occurred naturally, such as radium and thorium. But in 1932, the Joliot-Curies discovered that they could make from an element which did not emit any type of radiation, a radioactive form. Soon after this, the development of the cyclotron by Ernest O. Lawrence and his associates made it possible to manufacture radioactive forms of nearly all the elements in the periodic table. During the war, the atomic pile was developed, and it provided an additional means for manufacturing large quantities of many of the radioactive elements. So from the cyclotron and pile, it is possible for the biologist and medical man to obtain practically any radioactive isotope which he needs in his work. Thus there are available two new fields for the medical man and biologist. First, another application of the tracer technique is available, since the radiations emitted by these elements, whether they be iron, or sodium, or any other, enables the investigator to trace that element

* Presented in the 22nd Graduate Fortnight at The New York Academy of Medicine, October 10, 1949.
** From the Division of Medical Physics, the Radiation Laboratory and the Department of Physics, the University of California, Berkeley.

in the intact animal or living person or in the test tube in the laboratory, because the radiations emitted by the element, which element retains its normal chemical characteristics, enable him to locate it and follow it. The heavy isotope tracer technique was limited to a few elements only, but now the whole periodic table was opened up. The second result of the discovery and production of artificial radioactivity was that here were new sources of radiation for therapy; in other words, previous to artificial radioactivity, there were x-rays and gamma rays, beta rays, and alpha particles from radium, but now we had these radiations and others from the nuclei of the artificially produced radioactive isotopes.

The nature of the radioactive isotope is such that it differs from its sister only in that it emits radiation and has a different atomic weight. Chemically it is no different. But it immediately becomes possible to determine the rate of absorption of various elements such as iron, sodium, copper, and iodine, in extremely small quantities or tracer doses, and to differentiate in the tissue by extremely sensitive means, the element that had been administered to the animal during previous hours, from the amount of that element which was already present. Soon several techniques for their use in such studies were developed. First, there is the so-called *in vivo* technique, in which a labeled or radioactive material or compound is located and measured in the living animal by means of counters placed over various parts of the body; second, sections of tissues are placed on sensitive x-ray films, and autoradiographs obtained of the site of deposition of the element in that tissue; third, the sample of tissue, urine, or blood from a subject or animal is measured in the test tube or crucible under the counter at various intervals after the administration of the radioactive material. It was thus possible to get a dynamic picture of metabolism. In addition to the stable isotopic tracer technique, which was limited in its application to a few elements such as hydrogen, carbon, oxygen or nitrogen, the tracer technique was now extended to all the elements in the periodic table and the sensitivity of the method was much greater than the sensitivity of the methods using heavy or stable isotopes.

The production of artificial radioactivity and its use in animals and humans had, long before the development of the atomic pile, introduced to the medical profession a new problem, since it had been known for a long time that radiations generally are damaging to tissue. Imme-

diately it became important for anyone intending to work in this field to note that radiations in general are destructive. Before attempting to use any of these artificially produced radioactive tracers in humans, it was important to refresh one's knowledge of the dangers of immediate or delayed effects of radiation, and to remember the story of the radium dial painters who tipped their tongues with radium paint and thereby had deposited in their bones extremely small quantities of radium and later developed anemia, osteonecrosis and osteogenic sarcomas.[1] In our early work we felt it very important that physicists be constantly reminded of the dangers of these new radiations, and the first biological experiments were planned to emphasize these dangers.[2]

All of us receive penetrating radiation in the form of cosmic rays and gamma rays from radium and other natural radioactive elements in the earth. Day in and day out, we are being irradiated with small doses. Over a period of years, we have learned that although in general radiation is damaging, there apparently is a safe amount of radiation which one can receive. It is important to remember also that radiation is damaging if long continued in small doses or received in single large doses. However, in contrast to natural radioactivity, where materials with long half lives are deposited in the body, we have in the artificial series, radioactive elements with relatively short half lives which do not become deposited permanently in the body. There are a few exceptions, such as radioactive strontium and plutonium. The former is a fission product and the latter a fissionable material. These and many other fission products when they gain entrance into the body become deposited in the skeleton and remain there for long period of time.[3] Brues and others have shown that tumors, such as osteogenic sarcomas, can be induced by these elements in animals, and probably tumors would also result if they were introduced in sufficient dosage into humans.[4] But in general, with most of the artificial radioactive materials the half lives are short as compared to the half lives of plutonium, strontium and radium. The half lives are weeks or months instead of hundreds of years. In general, they do not become permanently deposited in the body, and it is possible to carry out tracer experiments with many of them in animals and man using what we call a "safe tracer dose." In Table I are listed several interesting radioactive elements and their safe tracer doses, calculated as the amount which will deliver to the body less than 0.1 roentgen of total body irradiation in a 24 hour period.[5, 6]

TABLE I

Atomic Number	*Isotope*	*Half Life*	*Safe Tracer Dose (microcuries)*
1	H^1	Stable	
1	H^3	10.7 years	29,000
6	C^{12}	Stable	
6	C^{14}	4,700 years	2,300
7	N^{15}	Stable	
11	Na^{24}	14.8 hours	210
15	I^{132}	14.3 days	168 soluble 20 colloid
26	Fe^{55}	4 years	1.5
26	Fe^{59}	47 days	75
53	I^{131}*	8 days	0.2

* I^{131} was discussed by Dr. Rulon Rawson during the second lecture of the evening.

There have been since 1934 numerous investigations in experimental medicine with radioactive isotopes, and isotopes of more than 50 different elements have been employed in these investigations.[6] I think it is of interest to point out that each of the several groups in a laboratory such as ours, feels that there are enough important problems to be attacked with each of the isotopes that all three floors and the clinical investigation ward could be turned over to working with one isotope only. Indeed, each of my associates working with iron, phosphorus, carbon, or iodine would like to take over the whole laboratory as far as space is concerned. Since there are now 98 elements in the periodic table, the field is thus quite a large one. Obviously, it would be impossible to discuss all of the work which has been done with these up to the present time. Here I will discuss chiefly several investigations from my own laboratory and hope that these will provide examples of isotopes in the study and treatment of disease. Table I refers to several isotopes with which we are now working, particularly H^3, C^{14}, P^{32}, Fe^{59} and I^{131}. I should first like to tell you about some current investigations with P^{32}.

P^{32} has been used perhaps more widely than any other isotope. There is one series of investigations now in progress in various laboratories and hospitals which I think has great clinical interest. This is the

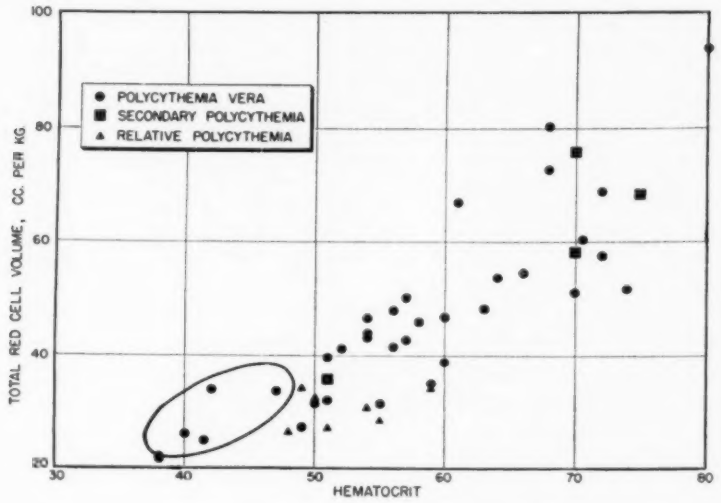


Fig. 1—Hematocrit and red cell volume in polycythemia.

use of P^{32} labeled red cells in the determination of blood volume. This technique is based on the early investigations of Hevesy.[7] If one takes blood from a normal subject or from a patient and incubates it for two hours with an isotonic solution of sodium radiophosphate, over 40 per cent of this labeled phosphate will enter and label the red cells. It is possible, therefore, by re-injecting this sample of red cells into the subject, to determine the blood volume by the simple dilution technique, comparing the counts of the diluted phosphate labeled red cells with the standard. Then with the aid of the hematocrit, one can determine the total red cell mass, total plasma volume and total blood volume.[8] At the present time, this is the only accurate and also relatively simple method for the determination of blood volume, and it is finding wide usefulness. We have done several hundred blood volume determinations on normal subjects and on patients with various pathological states, including polycythemia vera, secondary polycythemia, chronic and acute leukemia, and various miscellaneous conditions such as nephritis, cirrhosis, pernicious anemia and cardiac failure. We have been struck with the fact that in a very high percentage of the patients the total

TABLE II—RED CELL TURNOVER IN SURGERY FOR TUBERCULOSIS

Patient	*Operation*	*Pre-op. TRCV*	*Post-op. TRCV*	*Transfusions whole blood*	*TRCV loss*
L.A.	Pneumonectomy	1440 cc.	1079 cc.	2000 cc.	1160 cc.
C.S.	Lobectomy	1563	746	3000	2020
C.D.	Thoracoplasty	1240	1276	1000	360
J.C.	Thoracoplasty	2024	2022	1500	600
M.V.	Thoracoplasty	2078	1797	1000	680

red cell count does not give us an accurate picture either of the red cell mass or the plasma volume of the particular patient in whom we are interested.[5] I think this is brought out very well in Figure 1 which shows the red cell mass determined by this technique plotted against the hematocrit. The great variation in the relationship between these two values is noted. If the hematocrit is to be of real value, it should give you information regarding the red cell mass, but it very often does not do this. It is seen here that a patient who has a hematocrit of 45 per cent may have a red cell mass varying from 25 cc/kg all the way up to 45 cc/kg. One would not detect this from the red cell count or hematocrit. This very often is due to the fact that one patient with a hematocrit of 45 per cent may have a very large plasma volume. In this case, his hematocrit actually represents a very large red cell mass compared to the other subject. Aside from its general implications, we have found that in the control and handling of patients with polycythemia vera, it is extremely important that we do red cell mass determinations and not depend upon the red cell count in determining the diagnosis, results of therapy, or the indications for further therapy. In a group of patients with chronic leukemia, there again is also a wide spread in the relationship between red cell mass and hematocrit. Surprisingly enough we have found that a very large number of patients with chronic leukemia with low red cell counts have a normal red cell mass. This has been found to be due usually to a high plasma volume. At first we thought the high plasma volume was characteristic of chronic leukemia, but it does not occur in every case. In those patients who have high plasma volumes, an enlarged spleen is always found associated. Very often we may have a patient with chronic leukemia who has a red cell count of 3.5

TABLE III
THE DILUTION OF STERNAL PUNCTURE BY PERIPHERAL BLOOD

Patient	*Diagnosis*	*Peripheral Blood in Sternal Puncture*
L.V.	Polycythemia	83%
L.Y.	Polycythemia	100
H.K.	Polycythemia	77
W.H.F.	Lymphatic Leukemia	87
W.H.M.	Lymphatic Leukemia	93
M.E.B.	Lymphatic Leukemia	84.5
G.F.	Myelogenous Leukemia	43.3
L.W.	Myelogenous Leukemia	36.1
A.G.	Myelogenous Leukemia	58.8
H.L.	Multiple Myeloma	97

million who is not having symptoms from anemia, and determination of the red cell mass shows it to be normal because there is a very large plasma volume.[9] Table II shows some interesting data on red cell mass in patients operated on for various surgical conditions. In all of the clinical states mentioned above, we have found this lack of a consistent relationship between hematocrit and red cell mass, and consequently we believe blood volume determinations will come to be used more and more in the handling of various medical and surgical conditions.

In summary, I think we can say that radioactive phosphorus has given us a very reliable and simple method for the determination of blood volume, and we are impressed with the usefulness of blood volume determinations in the handling of various clinical conditions. The red cell count and the hematocrit are often misleading.

Table III concerns another application of the labeled red cell technique using P^{32} labeled red cells, developed by Berlin in this laboratory.[10] In our clinic prior to a sternal marrow puncture, the patient's red cells are labeled with P^{32} and are re-injected 15 minutes before a sternal puncture is carried out. Then the marrow puncture sample and a blood sample are analyzed for radioactivity, and one can then calculate the dilution of the marrow blood with the peripheral blood. It shows the striking finding that in all marrow punctures, there is more or less dilution of the marrow sample with peripheral blood, and this fits in with the known unreliability of the marrow puncture, particularly with ref-

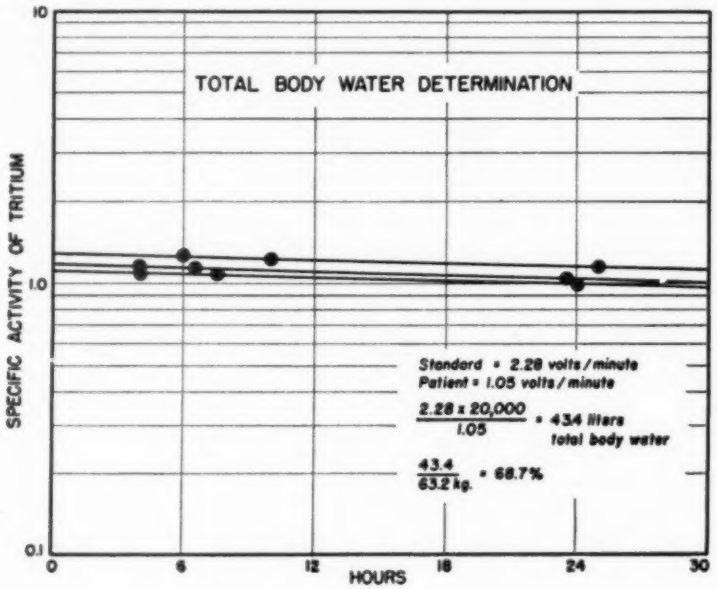


Fig. 2—Total body water in 3 patients.

erence to the total nucleated cell count, and also agrees with the known fact that often the marrow resembles peripheral blood. This gives us, then, an accurate method for determining the exact amount of blood that has diluted the marrow sample, so that one can correct for this in interpreting the findings.

Some further observations have been made with P^{32} labeled red cells and also with radioactive sodium, radioactive carbon monoxide and radioactive water (hydrogen 3, which has a half life of something like ten years). There already is evidence that the latter is going to be an extremely useful isotope in the study of body water in heart failure, kidney disease, and in other clinical conditions. Since the safe tracer dose of this material is known, it is obvious that here is a method for the quick determination of total body water by the dilution of the activity injected.[11] The first studies on patients have recently been completed[12] (Figure 2). One cc. of radioactive water is injected intravenously, blood samples are taken at intervals and by extrapolation, the dilu-

tion determined after subtracting excreted activity. Also of interest is the work that is being carried on by Pace and Strajman and their associates in this laboratory, using not only radioactive water but also radioactive carbon monoxide, radioactive sodium chloride, and P^{32} labeled red cells.[13] With the aid of these various labeled materials, their rates of mixing in normal subjects and in patients with cardiac disease, with and without edema, and in patients with nephritis with edema, have been studied. In general, the findings in the case of radioactive sodium have shown there are about 5 components to the mixing curves. The fastest component is about 30 seconds, the next fastest component 2 minutes, and then there are 3 slower components. The first 2 very fast components probably represent the mixing of the salt in the blood stream and the extracellular fluid. And finally, there is the long component of many days which is the rate of excretion. If CO is used, radioactive CO or ordinary CO, and similar samples are taken, there are again the 2 fast components in the normal subject and then another slow component of around 10 minutes which is possibly the disappearance of CO into myoglobin. Then there is the somewhat slower component of excretion of CO through the exhaled air. In other words, there are 4 components for CO. The slow component for CO, which has been suspected of going into muscle, has been checked by the *in vivo* counting method in which it has been found by placing a counter over the thigh, that the CO is disappearing into muscle. This gives us additional explanation for the unreliability of the CO method of determining blood volume, since some of the CO does apparently go into myoglobin. This would account for the fact that the CO blood volume method gives values about 20 per cent higher than the labeled red cell method for the red cell mass. If labeled red cells are studied, there are the 2 first mixing components and then a very slow component which results from the loss of the P^{32} from the labeled red cells and its excretion.

It is interesting that if these studies are done on cardiac patients, all of these components are slower, and indeed one would expect this, that is, for the patients in failure with or without edema. If the patients with edema are studied, and the curves are extrapolated, it has been found that about 23 per cent of the fluid is extracellular fluid compared to the normal of about 17 per cent. Patients with no edema but still with cardiac failure, do have the slower mixing times, but they have been

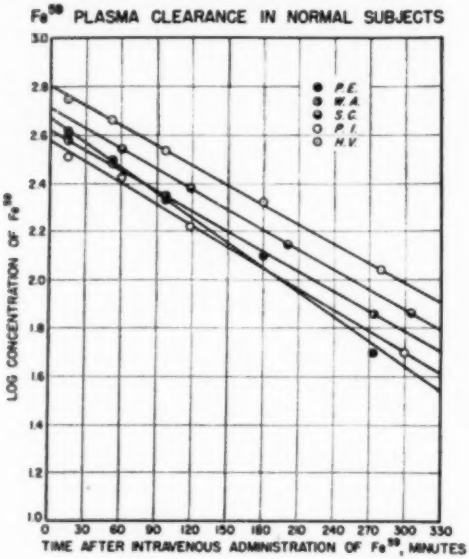


Fig. 3—Plasma iron clearance in normal subjects.

found to have a normal extracellular fluid space. On the other hand, in cases of nephritics with edema, where cardiac function is normal, they have all been found to have normal mixing times, but they have again been found to have a marked increase in the extracellular space. This gives a good method for measuring the dynamics of the circulation in health and in disease.[13]

Another radioactive isotope which is proving very useful is iron 59 which has a half life of about forty-seven days, and in our work it is made in the 60″ cyclotron by bombarding Co^{58} with deuterons. Although the total amount of iron in the body is not much more than 3 grams, it is so intimately tied up with the hemoglobin molecule and oxygen transfer that it is obviously important in normal and pathological processes. This isotope of iron emits both beta rays and gamma rays so that it is not only possible to measure the metabolism of iron by taking samples of blood, urine, stools or other tissues and measuring them directly, but also to study the turnover and uptake of iron in the

living human, because the gamma rays can be detected when counters are placed over various parts of the body. In our first studies, my associate Dr. Rex Huff,[14] measured the rate of utilization of iron in the normal subject. This was done by injecting intravenously a so-called tracer does of radioactive iron. (This was usually a total of about 30 micrograms of iron chloride, carrying an activity of a few microcuries.) By taking blood samples every hour for several hours and measuring their activity, the rate at which iron disappeared from the plasma was measured. Figure 3 shows typical curves of five normal men, ages 40-60. The log of the counting rate from the blood sample is plotted against time in minutes. All five curves are more or less parallel, indicating that these normal individuals use iron, i.e., clear their plasma of iron, at about the same rate; or half of their plasma iron is cleared about every two hours. Taking the half life of these curves, which run on the average of about two hours for the normal person, and knowing the actual plasma iron concentration, that is, the total plasma iron, which usually runs one microgram per cc., it is possible to calculate the number of milligrams of iron cleared from the plasma per hour or per 24 hour period. For example,

$$\% \text{ cleared per 24 hours} = \frac{0.69}{\text{half life}} \times \text{ucgm/cc} \times \text{plasma volume} \times 24.$$

This group of five normal men cleared from 21 to 30 milligrams per day with an average of 27 milligrams.

Previously it was known that when iron was injected intravenously into normal human subjects or into patients, more or less of that iron eventually found its way into the red cells, presumably a part of the hemoglobin of the red cells. Thus we have here a method of determining the amount of iron used in red cell production in a 24 hour period by a normal individual, simply by multiplying the amount of iron cleared per unit time by the percentage of iron going into the red cells during the same period of time. In this way, one can state the number of milligrams of iron being incorporated into red cells per 24 hour period. We have here, then, a test of the rate at which iron is being metabolized. It might be called a *bone marrow function test* or an *iron utilization test*. Knowing that red cells in general contain about 1 milligram of iron per cc. of red cells, and measuring the red cell mass, it was then possible to calculate the percentage of the red cell iron re-

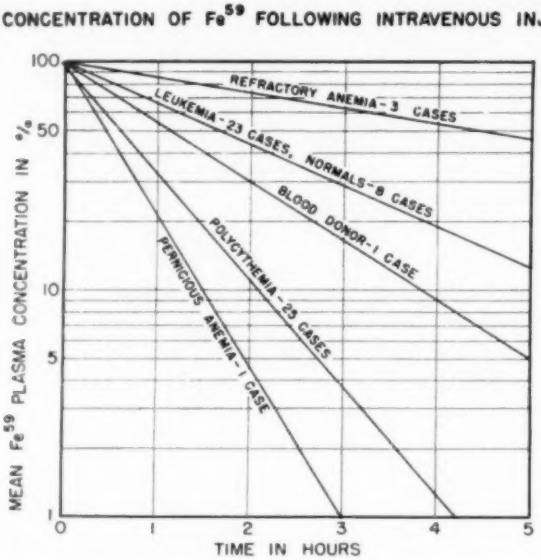


Fig. 4—Plasma iron clearance in various hematologic conditions.

newed in a 24 hour period. This came out to be about .85 per cent per day which fits the known life of the normal red cell—average life of 120 days—as shown by Shemin and Rittenberg in their studies with N^{15} labeled glycine.[15] Their work gave a check on this method for measuring the rate of hemoglobin incorporation and red cell production.

It was then of interest to study the rate at which iron was cleared from the plasma and incorporated into red cells under various pathologic states. Figure 4 shows the difference in the rate of clearance of the plasma iron in normal subjects and in patients with refractory anemia, polycythemia vera, leukemia and pernicious anemia, and one normal patient who had been a frequent blood donor previously. In the polycythemic group, clearance is very fast, the half time being in some cases as short as 20 minutes; whereas the aplastic anemia group shows a very slow clearance of iron from the plasma and little incorporation of iron into the red cells. In a group of polycythemia patients, it was found that many of them made iron into red cells so fast that they were replacing as much as 4 per cent of their red cell mass per day, instead

of the normal .85 per cent. It is interesting to find, however, that in patients with extremely high red cell counts secondary to congenital heart disease, red cells were replaced at a normal rate, i.e., they might have a very high red cell mass, but they had reached equilibrium and were replacing the normal .85 per cent of these red cells per day instead of the very fast rate of replacement of red cells in polycythemia vera. We have likewise found the same situation to hold in a study of the secondary polycythemia of the Peruvian Indians living in the high Andes.* These findings have forced us to conclude that patients with polycythemia vera must have a rapid destruction of red cells at times, since the high rate of replacement of red cells could not go on indefinitely without an unlimited rise of the red cell mass and red cell count. We are now in the process of determining the life of the red cell in this disease with radio glycine;[16] and indeed, Shemin, Rittenberg and London and the late Dr. Randolph West did this with N^{15} labeled glycine in one patient with polycythemia and found a normal red cell life.[17] This cannot hold, always, since if it did, the patient would continue to build red cells and the hematocrit and red cell mass would increase indefinitely. There must at times be increased destruction of red cells in these patients to compensate for the abnormally rapid rate of production (Figure 5).

In patients with leukemia there are other interesting findings. It is found that although they may be very anemic, nevertheless they seem to be manufacturing red cells at a normal or a very rapid rate. Some of them clear as much as two or three times as much iron into the red cells as a normal person. This suggests the possibility that the anemia in many of these patients with leukemia is not due to the failure of red cell production, but must be due to a relatively short life of the red cell. All of us have seen patients with leukemia who are hemolyzing transfused cells or are hemolyzing their own cells, but these are rare. Most of us think of leukemia as a disease in which the red cell production is interfered with by leukemic infiltration of the marrow. However, in many of the patients with leukemia studied, nearly all have a normal or rapid rate of iron incorporation into red cells. This gives us something to think about with reference to the etiology of the anemia of this disease. Not only is there then an apparently rapid white cell production in leukemia, but there may also be a rapid rate of red cell production.

* An expedition to study the polycythemia of the Peruvian Indians in the Andes, Feb.-March, 1950. (In preparation.)

FIGURE 5—PLASMA IRON TURNOVER AND HEMOGLOBIN PRODUCTION IN VARIOUS PATHOLOGICAL CONDITIONS AND IN NORMAL SUBJECTS

Diagnosis		*Plasma Iron Turnover*		*Iron for Hemoglobin Synthesis*		*Percent Hemoglobin Renewed Per Day*
		mg./day	*mg./day/kg.*	*mg./day*	*mg./day/kg.*	
Poly. Vera	MH	245	3.7	165	2.4	3.70
Poly. Vera	Ltl	30	0.44	25	0.39	1.30
Poly. Vera	Ktr	42	0.51	32	0.39	0.93
Poly. Vera	Fin	35	0.52	25	0.37	1.25
Poly. Vera	Pchr	43	0.61	42	0.59	1.36
Poly. Vera	Rnl	76	1.33	70	1.23	2.46
Poly. Vera	Rbtsn	135	2.10	86	1.34	3.62
Poly. Sec.	Syk	26	0.36	18	0.25	0.86
Splenomegaly	Schm	220	2.89	17	0.22	1.11
R. Anemia	Pkr	127	1.74	4	0.05	0.40
R. Anemia	McD	13	0.26	0.13	0.003	0.01
Myel. Leukemia	Ptrs	20	0.36	6	0.11	0.48
Myel. Leukemia	A Jms	48	0.55	30	0.35	1.50
Splenomegaly	Haly	46		33		1.76
Myel. Leukemia	Hldn	33	0.43	5	0.065	0.45
Normal	Perr	28	0.39	20	0.28	0.74
Normal	Wad	30	0.40	20	0.26	0.72
Normal	Sch	20	0.31	14	0.22	0.76
Normal	Piet	37	0.32	31	0.26	1.01
Normal	Hut	21	0.31	15	0.22	1.03
Blood Donor	Ave	30	0.42	25	0.36	1.26

Studies on pernicious anemia using the same technique also are of interest. Patients with extremely low red cell masses and red cell counts untreated with vitamin B-12 or liver actually are clearing their plasma very rapidly of the labeled iron, and it appears in good quantities in the red cell mass. Ordinarily we think of a red cell maturation arrest in pernicious anemia, indicating that iron is not going into the manufacture of red cells; but in these preliminary studies we find that this is not true. The iron is going into the red cells, but there must be something abnormal about the length of life of the red cells which are made. Perhaps this fits in with the well-known fact that patients with pernicious anemia in relapse do have an abnormal pigment metabolism. Their icteric index and serum bilirubin are often high, and there is increased pigment in

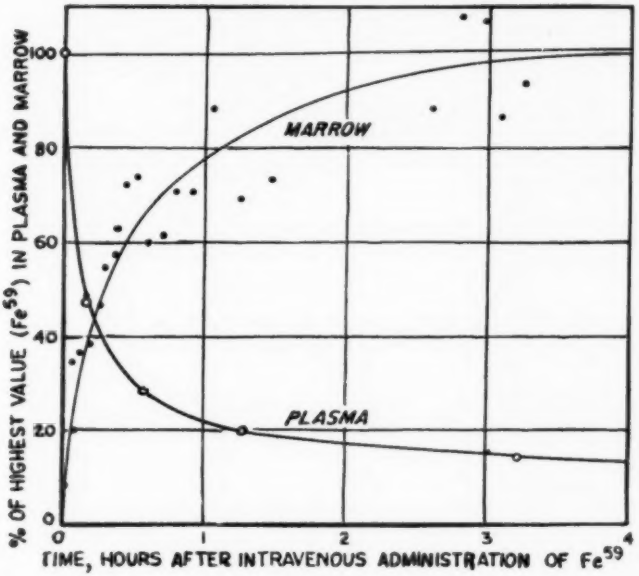


Fig. 6—Plasma clearance of iron and its appearance in the marrow of the femur. (Counter looking from head of femur along its length).

the tissues and stools. About a year ago, Singer and his associates showed that if blood from pernicious anemia patients was transfused into normal persons, these red cells did have a relatively short life duration.[18] Perhaps the anti-anemia therapy gives the red cells a normal life duration and is not primarily concerned with red cell production.

Finally, the movement of iron in the body has been studied by placing counters over various parts of the body, after a tracer dose of iron was given intravenously. At the same time, plasma iron samples are taken and counted, so that, in addition to a disappearance curve, we have an uptake curve in various parts of the body (Figure 6). This shows the disappearance of the labeled iron from the plasma of a patient who had a very active polycythemia vera who was manufacturing red cells at a very rapid rate. It is seen that the half time of disappearance of iron from the plasma is about 20 minutes, many times the normal rate. A counter was placed at the head of the femur looking at as much of the femur as possible. The gamma ray counts gradually increased,

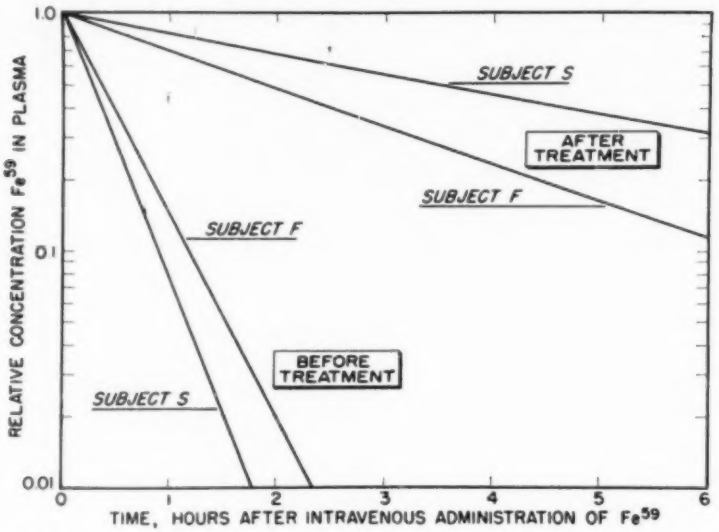
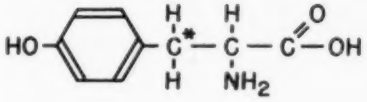


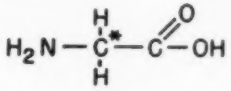
Fig. 7—The depression of iron turnover by P^{32} in two patients wiht polycythemia vera.

with the rate of increase approximately the same as the rate of decrease of the plasma iron. Here then in the living subject iron is seen to go out of the plasma and into the marrow. From the marrow, the iron appears in the peripheral blood in the form of iron in the hemoglobin of the red cells. This then is a method of assessing the movement of iron in the body. With the use of this test, it is possible to get a picture of the way the body is handling iron. It will be possible, for instance, in the case of a patient who is not making red cells normally, to predict the development of an anemia in that person perhaps a month or two ahead of the actual appearance of that anemia. We are finding in patients with polycythemia, that long before a high red cell count develops, an overactive marrow can be detected by a fast iron clearance, and the patient can be treated accordingly. One thus prevents a marked rise in the red cell count and red cell mass (Figure 7). Also, we are finding it useful in the handling of patients with leukemia, since in the patient who stays in remission, the incorporation of hemoglobin into red cells is often not as rapid as in the patient who is not doing well, but falls to more nearly normal levels.

TYROSINE (β-[p-hydroxyphenyl]-α-aminopropionic acid)



GLYCINE (aminoacetic acid)



STILBAMIDINE

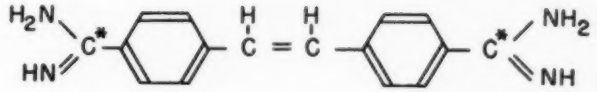


Fig. 8—Compounds labeled with carbon 14.

A fourth radioactive isotope of great value is carbon 14, particularly in relation to labeled compounds, such as hormones, vitamins, carbohydrates, proteins, fats, antibiotics, cancerogenic hydrocarbon, etc., which are built from or labeled with a radioactive element. Fortunately, we have in the laboratory a group of chemists who are doing this. Figure 8 shows several of these compounds labeled with carbon 14. In this work, they start out usually with radioactive CO_2, go through the synthetic procedures, and arrive at the compound desired. My colleague, Dr. Hardin Jones, has been using many of these labeled compounds such as organic and amino acids and glucose in the study of metabolism in small animals. For example, he has studied the rate at which animals exhale labeled carbon dioxide after they have been given intravenously various labeled materials. With certain of these labeled acids, the curve of elimination in normal and tumor animals is the same. Now if the radioactive carbon were labeled in the methyl position or in the carbon position, the curve of elimination in the tumor animals would be similar to the control group; but when the label is moved over to the carboxyl-carbon position, this curve of elimination is quite different.

By this technique, it is possible to detect the presence in a mouse of an extremely small transplanted mammary tumor, indicating that qualitatively or quantitatively the metabolic pathway of the oxidation of this organic acid is different in tumor animals from that of the normal animals.[19]

In this connection, the investigations of Dr. Lola Kelly are of interest. In this work, the radioactive isotope P^{32} is used. After three years of work studying the metabolism of nucleic acid in normal and tumor animals, just recently she has unexpectedly found that the presence of an extremely small mammary tumor in a mouse indirectly stimulated the metabolism of desoxypentose nucleic acid as measured by P^{32} turnover in some of the normal tissues.[20] These normal tissues, then, are indirectly affected by the presence of this tumor in that they turn over this nucleic acid much more rapidly than normally.

A more recent example of the labeling of organic compounds is the work of my colleagues, Gofman et al[21] in which two physical tools, the ultracentrifuge and the radioactive isotope, have been used in the study of atherosclerosis in animals and in man. The sites of deposition in atherosclerotic rabbits of lipoproteins labeled with P^{32} and of cholesterol labeled with H^3 are being studied.[21, 22]

Radioactive sodium has been mentioned already and has been used extensively by numerous workers in various physiological investigations. Particularly in connection with the circulation, certain studies have proved to be of great interest, and Dr. Quimby here in New York has been one of the leaders in this work. We have found radioactive sodium and the various radioactive inert gases of interest too, in the study of circulation to the extremities, and Figure 9 brings out some of these points. Here we see the hand radioactive krypton uptake curves of a normal subject under various environmental conditions. With room temperature of 24 degrees, the uptake curve in the hand is very flat; whereas following ten minutes of exercise or with a skin temperature of 31 degrees, the curve is much steeper, as it also is when the patient has received 10 minutes of diathermy.[23] Also, the work on the dynamics of the flow of blood through the chambers of the heart is of interest.[24] In the laboratory, two counters are placed over the heart, one over the right and one over the left, and a tracer dose of 200 microcuries of sodium 24 as a normal saline solution is injected into the antecubital vein. The curves of appearance of sodium in the right heart and in the left heart

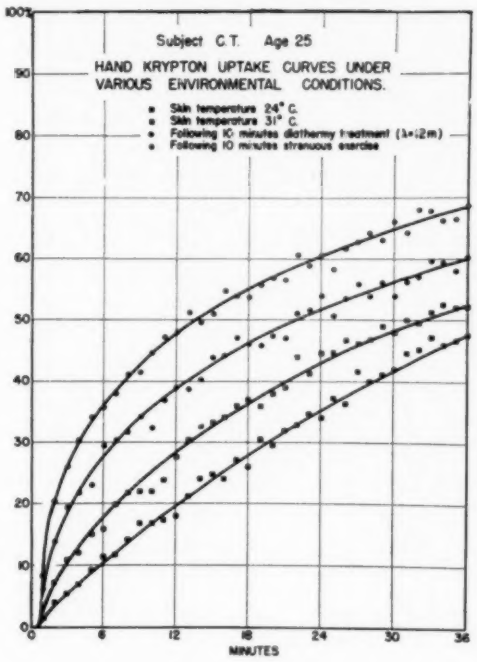


Fig. 9

are determined. I think this technique may prove to be very valuable, although at the present time, it is too crude. Extensive experience with it during the past six months, indicates that it has not reached the point of diagnostic usefulness nor has it proved to be extremely useful even in the study of various abnormal or normal cardiac states. The two counter technique gives us simultaneous R and L curves in cases of a patent septum between the right and left heart.[24a]

Another example of the application of isotopes is brought out by the work of my colleague, Dr. Tobias, who has recently applied a technique for measuring extremely small amounts of elements in tissue samples.[25] I believe this technique will be extremely valuable in trace analysis in the fields of pharmacology and toxicology where it is important to detect the presence of very small amounts of elements. This

FIGURE 10—DETECTION LIMIT OF ACTIVATION ANALYSIS*

Element	*A*	*Sensitivity*
Na	23	2.4 x 10^{-9}
P	31	6.4 x 10^{-9}
K	41	4 x 10^{-8}
Ca	44	2.2 x 10^{-7}
Sc	45	1 x 10^{-10}
Cr	50	5 x 10^{-9}
Mn	55	1.8 x 10^{-9}
Fe	58	2.5 x 10^{-6}
Cu	63	2.1 x 10^{-9}
Zn	64	4 x 10^{-8}
As	75	1.2 x 10^{-9}
Br	81	4.8 x 10^{-9}
Mo	98	6.5 x 10^{-8}
Rh	103	0.4 x 10^{-10}
Ag	109	1.6 x 10^{-8}
In	113	2.8 x 10^{-9}
Sb	121	1.2 x 10^{-9}
Te	126	5.5 x 10^{-9}
I	127	1.3 x 10^{-9}
Cs	133	2 x 10^{-9}
Ba	138	2.5 x 10^{-9}
Dy	164	0.15 x 10^{-10}
Pt	196	2.2 x 10^{-8}
Au	197	2.7 x 10^{-9}
Hg	202	2.6 x 10^{-8}

* Clinton Pile.

technique enables him to detect the presence of certain elements such as gold, manganese, iron, zinc, iodine, and many others, with a sensitivity which may be many times that of any other standard procedure for microchemical analysis. The method consists of placing the sample of biological material in the atomic pile, leaving it there for a desired period of time so that any trace element in the sample can be caused to become radioactive. This technique is called the technique of trace analysis by means of induced activity. After the ash is removed from the pile, various carrier amounts of the element which are of interest to the investigator are added and then extracted from the tissue and the

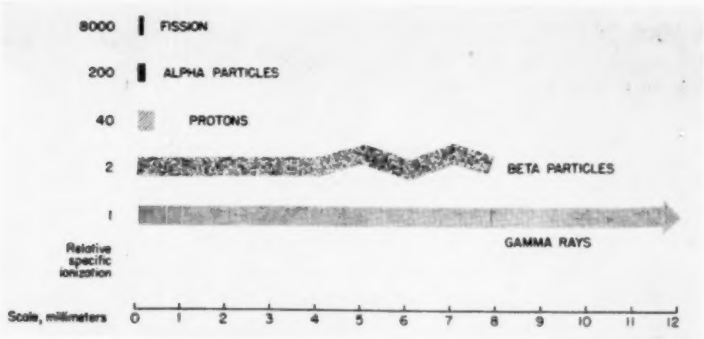


Fig. 11—Penetrating power of rays in cm. of tissue.

radioactivity of the sample is determined. Knowing the activity induced in a monitoring sample, it is possible to calculate the total amount of that element present in a gram of tissue ash. Figure 10 shows the amounts of various elements which can be detected in this way.

In looking for therapeutic applications of all of these new radioactive elements, the problem is the same as in the use of x-rays and radium: to deliver to the desired tissue as much radiation as possible with minimal dosage to the normal surrounding tissue. In other words, the problem is to find radioactive compounds or materials which might selectively localize in the tissues you desire to radiate. In attempting to use radiations therapeutically, it is important to remember that various types of radiations have different qualities and characteristics. For example, Figure 11 shows the penetrating power of several types of rays in terms of cm. in tissue. This may be from one or more cell diameters to many feet, such as in the case of the 180 mev. neutrons coming from the big cyclotron, which travel 12 or more feet in tissue or tissue-like materials. Thus, ideally, in radiation therapy by selective localization, one would prefer to have a radioactive compound which would localize in the neoplastic cell only and which would emit a ray which dissipates all of its energy in one cell diameter.

First, I would like to discuss with you radioactive phosphorus. This element, which emits beta rays and which was really the first widely available radioactive element, has a half life of approximately two

weeks. It was early found that when given intravenously or orally to animals, it localized in rapidly growing tissues and in bone and bone marrow. Of course, this was to be expected because of the fact that growing tissue needs phosphorus for the manufacture of nucleo-protein, and bone, of course, having a high phosphorus content, would also take up a considerable amount of phosphorus when given in the form of some soluble compound such as sodium acid phosphate. We have carried out numerous investigations on the metabolism of phosphorus in normal and neoplastic tissues in animals, studying various tumors, including lymphomas, lymphosarcomas, and mammary carcinomas, and have always found that tumor tissue took up more of the labeled isotope than any other soft tissue, and that bone and bone marrow always ended up with high activities also. These experiments were also extended to human beings where small non-damaging amounts of sodium radiophosphate were given, usually to patients with advanced cancer; and in various types of tumors it was found that the tumors always had a very high uptake compared to normal tissues, but bone and bone marrow always ended up with even larger activities.

In these early investigations, we realized that if we were looking for therapeutic applications of radioactive phosphorus we must be interested only in those diseases which involve soft tissue growth where there was also bone marrow involvement, since the only selective radiation that you could obtain with phosphorus would be in the marrow and in rapidly growing tissue. Prior to any clinical investigations, it seemed desirable to find out something about the radiation effects of varying doses of radioactive phosphorus on animals, and a series of investigations was carried out on mice, rats, and monkeys. The doses necessary to produce a leukopenia or an anemia or both were determined and the lethal dose was likewise determined.[26] Extensive studies were also carried out on mice with leukemia. Although we knew we could not deliver a lethal dose to the tumor cells by means of P^{32}, an attempt was made with moderate doses to see whether the lives of the animals with leukemia could be prolonged, or whether they could be cured. In these experiments, we found that in a large series of animals treated with divided doses, about 15 per cent of them survived the treatment and were rid of their disease. This was rather surprising because we were unable to demonstrate any selective sensitivity of the tumor cells and leukemic blood cells over the normal cells.[27]

We felt very strongly that no artificial radioactive material in therapeutic doses should be used in any patients other than those with a relatively short life expectancy; therefore, in the absence of a satisfactory method for the treatment of human leukemia, we thought it justified to begin an investigation of this disease. In our early work, numerous tracer and therapeutic studies were carried out on patients with acute leukemia and terminal chronic leukemia, and this confirmed our findings in animals that radioactive phosphorus when given in a soluble form either orally or intravenously, did become concentrated to a relatively high degree in rapidly growing leukemic tissue and in bone marrow. It was also found that P^{32} when given orally or intravenously had a very high uptake in the body—from 60 to 80 per cent—and that the rate of excretion in the urine or stools was relatively slow. Taking into consideration both excretion and decay, it was determined that a millicurie of P^{32} in the body would deliver throughout its life in the body approximately 6 r of radiation. Thus we were guided in dosage, and it was possible to give doses of this material comparable to doses of x-ray given to leukemic patients in terms of roentgens of radiation to various tissues. Thus with the background of clinical experience in the treatment of leukemia with x-ray, both local and of the total body, and with our background of experience on the effects of P^{32} on the blood and tissues of animals, we were able to start out these investigations using comparable doses of radiation. All that we could hope for in this work was to get some improvement in the end results with the relatively greater delivery of radiation to the involved tissues. We knew from the very beginning that since there was no greater sensitivity of the leukemic cells over the normal cells, and since we could not get a very great localization of the P^{32} in the leukemic cells alone, we could not cure the disease. The dosages have varied considerably, but in general they have approximated a total body irradiation of from 10 to 200 roentgens. The end results are somewhat better than those previously reported after other methods of therapy.[28, 29]

An associate, Dr. Moffitt, and I have studied further some of these patients in an attempt to predict which patients will do well. Several interesting findings have appeared. For instance, in the patients with chronic lymphatic leukemia, we have found that with one exception all of the patients with the longest duration of the disease are men. This is brought out in Table IV, where the average duration of life is 8.4

TABLE IV

CHRONIC LYMPHATIC LEUKEMIA					CHRONIC MYELOGENOUS LEUKEMIA				
Case	*Sex*	*Age at Onset*	*Age at Death*	*Duration*	*Case*	*Sex*	*Age at Onset*	*Age at Death*	*Duration*
FAB	M	39	—	7.6	IA	F	49	54	5.5
FMB	M	56	67	11.2	DEF	F	35	40	5.3
AB	M	49	57	7.8	MG	M	39	45	5.9
BC	M	34	40	6.6	FG	F	20	26	6.0
LPD	M	50.3	—	19.7	EH	M	32	36	6.0
FE	M	40	—	5.3	MLI	M	43	—	5.6
KCG	M	36	42	5.4	IJ	F	44	—	6.8
GEH	M	66	73	7.9	WCJ	F	29	35	5.2
FHL	M	65	74	9.0	CK	M	27	36	9.0
FWL	M	55	62	7.3	ALV	F	52	60	8.8
JFP	M	35	—	11.6	PM	F	11	—	8.3
MP	F	59	—	7.2	JM	F	53	59	6.3
BJP	M	54	—	6.0	MGM	M	26	32	5.5
CWR	M	50	55	5.4	THM	F	53	59	6.8
CRR	M	43	49	6.3	EP	F	32	38	6.0
GLS	M	37	—	11.6					
AVG.	1 F 15 M	48	57.7	8.44	AVG.	10 F 5 M	36.3	43.3	6.47

years, and some of these patients are still living. Approximately 70 per cent of the patients with chronic lymphatic leukemia are men, but the percentage of patients in this group who have the longest survival is significantly higher. Likewise, in the patients with chronic myelogenous leukemia, we have found that two-thirds of the patients with the longest duration are women. Since the highest incidence of the disease is in men—about 60 per cent of the patients being men and 40 per cent women—we have the reverse, about 70 per cent of the longest survivals are women and 30 per cent are men. We do not understand the significance of this finding, but it is possible that it indicates some hormonal factor and suggests the possibility of trying hormone therapy as an adjunct to radiation therapy.[30] This we are now doing, and the preliminary results do not rule out the possible effect of hormones on the course of the disease.

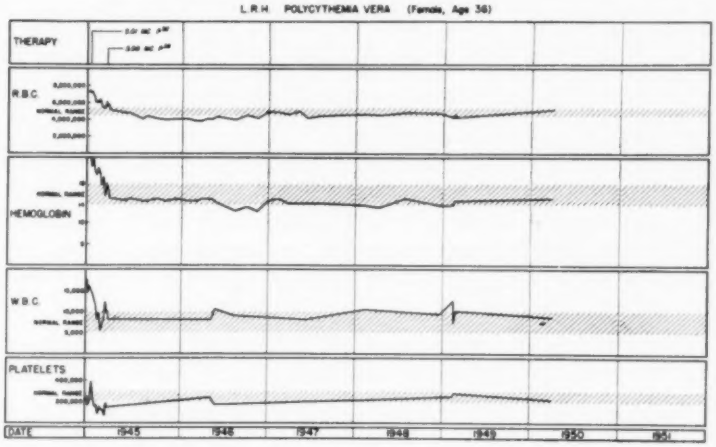


Fig. 12—Hematologic course of a 36 year old female patient with polycythemia vera.

I should like now to pass on to the studies we have carried out with the disease, polycythemia vera. These studies were begun in 1939, three years after the work with leukemia was started. At this time we were faced with the problem of the treatment of two patients with polycythemia vera who had very poor veins and could not be bled. Consequently, we had the decision to make: should we use phenylhydrazine, or should we attempt to treat these people with P^{32}? This was the only element at the beginning of these studies which was available and which seemed to be logical to use because of its great localization in the marrow. We knew, of course, that the other tissues, particularly the liver, spleen and lymph nodes, would receive irradiation too. In view of the fact that more and more patients with polycythemia vera were being treated with total body irradiation, there seemed no question but that P^{32} would be equally safe, and perhaps somewhat safer, since relatively smaller doses of radiation could be given to normal tissues as compared to the abnormal tissues, and since the total dosage delivered was less than with x-ray. Consequently we treated these two patients. Both of them with classical polycythemia vera, uncontrolled by venesections or phenylhydrazine, have responded very nicely to the infrequent administration of P^{32} during these ensuing ten years. Their symp-

toms have been relieved and their blood pictures have been kept at near normal levels with treatments given as infrequently as every three years, usually in the form of 1 or 2 doses of 3 to 5 mc., either orally or intravenously. At the beginning of treatment there is a depression of the white count and the platelet count, both of which return to near normal levels after the red count has fallen to normal ranges. Figure 12 shows the hematologic course of another patient, the remission in whom has lasted five years. Before describing further results in the treatment of this disease with radioactive phosphorus, and during the past five years with radioactive colloids,[31] I will summarize some of the clinical and laboratory and other findings in this group of patients.

The diagnosis of polycythemia vera was made from the history, physical examination and laboratory findings, including sternal marrow puncture and blood oxygen saturation. The degree of unexplained polycythemia had to be 7,000,000 or above before the diagnosis was made, unless there was clearcut evidence of the diagnosis in the past or an enlarged spleen with a definitely elevated red blood cell count. In borderline cases, the red cell mass as determined by P^{32} labeled red cells and the measurement of red cell production with Fe^{59} were often helpful in diagnosis. We have treated with radioactive phosphorus approximately 150 patients during the past eleven years. In many cases, the infrequent administration of P^{32} in small doses has satisfactorily controlled the disease, and in some cases a single course of therapy has produced a remission lasting several years. Other patients require more frequent therapy. On the average, treatment was necessary every three years. With reference to the causes of death, it is interesting that we have seen thromboses very infrequently—in only 3 patients out of the 24 who have died. One of these was a patient who was no longer under our care and who was being bled after a second elevation of his red count. Another patient died from circulatory failure following widespread thromboses which had developed before treatment with P^{32}. There have been three cases of carcinoma in different parts of the body which occurred soon after the beginning of therapy and probably were related to the normal incidence of neoplastic disease in patients of this age group. We do not see any relation between these cancers and their possible induction by radiation. With reference to the deleterious effects of radiation, there is no evidence in this group of patients or in the large group of patients with leukemia, lymphosarcoma, and other dis-

eases, who have received radioactive isotope therapy during the past fifteen years, that tumors are being induced. In fact, we have found in all of the patients with leukemia only two who have developed cancer. With reference to the genetic effects of radiation, it is interesting that, since the average age of onset of these patients with polycythemia is 50, in the non-childbearing age, we need not worry about any recessive mutations which might show up in later generations.[32]

With reference to the possible complication of leukemia, many workers believe that patients with polycythemia living long enough will always develop leukemia. Most of the literature reports that at least 20 per cent of the patients develop leukemia. It is interesting in this group of patients that we have had only 5 patients who have developed a terminal leukemia which has been a causative factor in death. It is of interest that 38 per cent of the patients when first seen have abnormal cells in their peripheral smears, that is, young cells, and of these only 27 per cent have had abnormal cells after therapy. This combined with the relatively low incidence of leukemia in this series has given us evidence that there is no increase in the complication of leukemia in polycythemia treated with radioactive isotopes, but there may well turn out to be a decrease or suppression of this complication. Certainly we have no evidence that this form of therapy is causing the complication to occur more frequently than after any other forms of therapy.[32]

In this series of polycythemia patients, their average age of onset was 50, and of the patients who have died, the average age at death has been 67, so this is an average life expectancy of seventeen years. It is interesting to compare this with the life expectancy in patients with diabetes treated with insulin and in patients with pernicious anemia treated with liver. In the diabetic group, the average age of onset is approximately 50 and the average age at death is 64, whereas in the treated pernicious anemia group, the average age at onset is 57 and the average age at death is 67, so we do have a favorable result when compared with the end results in these other two diseases.[32]

In summary, these are the results of the treatment of polycythemia and leukemia with artificially produced radioactive isotopes. They were obtained with an element which shows some degree of selective localization in the desired area, but not to the degree which one desires. One would like to find an isotope or compound with a very soft irradiation which traverses only one or two cell diameters and which could be

localized in the particular cell to be irradiated. An ideal isotope would be an alpha ray emitter which would travel only a cell diameter and would not pass through other normal cells, so that radiation to them could be avoided. One step in the direction of more selective localization in the treatment of myelogenous leukemia and in the treatment of polycythemia vera by the use of various radioactive colloids has been made by my colleagues, Jones[33] and Gofman.[31] These are various colloids of elements such as chromium, yttrium, and zirconium, having various particle diameters. They may be localized exclusively in the desired distribution between liver, spleen and marrow. At the present time, a series of patients with chronic myelogenous leukemia and polycythemia is being treated with these radioactive colloids, irradiating the marrow chiefly in the polycythemic group, and the liver, spleen and marrow in the leukemic group, without any appreciable irradiation to other normal tissues. One of the earlier colloids, chromic radiophosphate, localizes in the spleen and liver because reticuloendothelial cells, particularly of the liver, take out these particles as they go through after an intravenous injection.

In this group of diseases of the hematopoietic system, early attempts to treat Hodgkin's disease, lymphosarcoma and multiple myeloma were made, and we have treated approximately 100 patients with these diagnoses. Here again one must realize at the outset that there is little chance of doing much in these diseases because they are not diseases of the marrow, but diseases usually of the lymph nodes, and in the case of multiple myeloma involvement of the marrow is side by side with the presence of normal tissues, so that lethal doses of radiation to the plasma cells cannot be given without damaging the normal cells.[34] However, we have had a few unusually favorable results in two groups of patients, but in both of them unusually good results are sometimes seen after other methods of therapy. First, in the case of giant follicle lymphoblastoma, many of the patients we have treated with radioactive phosphorus are still living today, many years after treatment with P^{32}. We certainly do not recommend, however, that this disease be treated with P^{32} since such excellent results are obtained with x-ray, and we have no statistical evidence that the results we have obtained are superior to those following x-ray.

In the case of multiple myeloma, experience with 21 patients again has given us some unusually good results in about ⅓ of these people.

The average length of life of the whole group treated is three years. It would be difficult to prove that this is statistically significantly greater than the results after treatment of this group of people with x-ray. We have had little success with Hodgkin's disease and indeed we are not even attempting to treat it with radioactive phosphorus for the present. We are, however, giving palliative therapy to patients with multiple myeloma and to patients with lymphosarcoma using P^{32} alone or in combination with x-ray.

One more application of P^{32} in therapy is its use in the treatment of superficial skin cancer, by placing on it a small absorbent blotting paper cut to the size of the lesion to which has been pipetted the desired dose of sodium radiophosphate. The beta rays of this material will penetrate only a few millimeters of tissue so that it is possible to deliver over a period of 72 hours, 5,000 to 10,000 roentgens to the tumor and cause it to disappear, such as occurs after surgery or x-ray or radium. This is another method for the treatment of superficial skin cancers and has been used on over 400 patients with great success by Low-Beer.[35]

Finally, I should not close without mentioning the work that has been done on the treatment of thyroid cancer with radioactive iodine. It has been found that some patients with thyroid cancer will selectively pick up radioactive iodine in the cancer cells and their metastases, after oral administration of the material. It is interesting that many years ago the first two patients with thyroid cancer studied with radioactive iodine by Hamilton were found to have no uptake in the thyroid cancer tissue.[36] Consequently it seemed doubtful that there would ever be any application of radioactive iodine in the selective irradiation of thyroid cancer. However, Seidlin and Marinelli and others have shown that some patients have metastases which take up iodine, and selective irradiation therapy may be rendered these patients. A number of years must elapse for the final evaluation of this form of therapy for metastatic thyroid cancer, but certainly palliation with extension of comfortable life is already being achieved in many patients.[37] From experience gained during the past 10 to 15 years, there seems little question that if one can get localization of radioactive materials in cancer tissue—50 or more times the concentration in other, normal tissues—definite therapeutic benefit to hopeless cancer patients can be obtained, particularly if radio isotopes with soft beta rays such

as H^3 and C^{14} are used. One must admit, however, that only the lack of our understanding of cancer and hyperplastic disease and the lack of certainty that we will soon understand them completely has stimulated investigators to make therapeutic attempts in the field of artificial radioactivity as it is applied to neoplastic or hyperplastic disease. The results are not exciting, nor completely satisfactory, but they are worthwhile, and the spirit of our laboratory is that, although the major emphasis of the application of atomic energy and nuclear physics to biology and medicine must be to the understanding of physiological and pathological processes, nevertheless, one must remain alert to possible therapeutic applications to some of these diseases which are not understood and are not successfully treated at the present time.

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ESSENTIAL FAMILIAL HYPERCHOLESTEROLEMIA: CUTANEOUS, METABOLIC AND HEREDITARY ASPECTS*

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THE metabolic disorder characterized by an increase of the total blood cholesterol with normal proportion of esters, and an increase in the phospholipids, has been designated by a group of us as essential familial hypercholesterolemia.[1] While this term does not follow the classifications proposed by Thannhauser,[2] Montgomery,[3] and others,[4-6] it is more descriptive and useful.

While many pathological conditions have been known to be associated with xanthomatous deposits in the skin, the significance of the primary metabolic disorder has not been fully recognized. Too much emphasis has been placed on xanthoma tuberosum, xanthoma tendinosum, and xanthelasma. Altogether eight kindred have been studied in detail by my associates and myself. The largest kindred only will be discussed in detail here.

In this kindred there were four generations composed of 282 individuals available for investigation and the various sibships were large and coöperative. Thorough clinical studies in 159 of these are used for statistical analysis. This group of 159 includes all individuals found to have elevated blood cholesterol, and many others with normal levels. The examinations were sufficiently complete to exclude the more common causes of hypercholesterolemia, such as nephrotic syndrome, diabetes, hypothyroidism, pregnancy, jaundice, and disease of the liver. Our study included:

1. Medical history and physical examinations (rectal examinations were done only when suggested by the history; no vaginal examinations were done).

2. Urine was examined for albumin, sugar and urobilinogen. The sediment was examined if there was any albumin present.

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3. Electrocardiograms were done on twenty-one of the group that had elevated blood cholesterols and on eleven of the normals.

4. Basal metabolic rates were determined if there was any suggestion of hypothyroidism.

5. Diet diaries were kept for a period of time. The results were analyzed by competent dietitians and calculations of the cholesterol intake were made on 91 individuals.

6. Total cholesterols and cholesterol esters were determined on all. Phospholipids and total lipids were determined on all of the individuals in whom the blood cholesterol was increased, and on many of the normals.

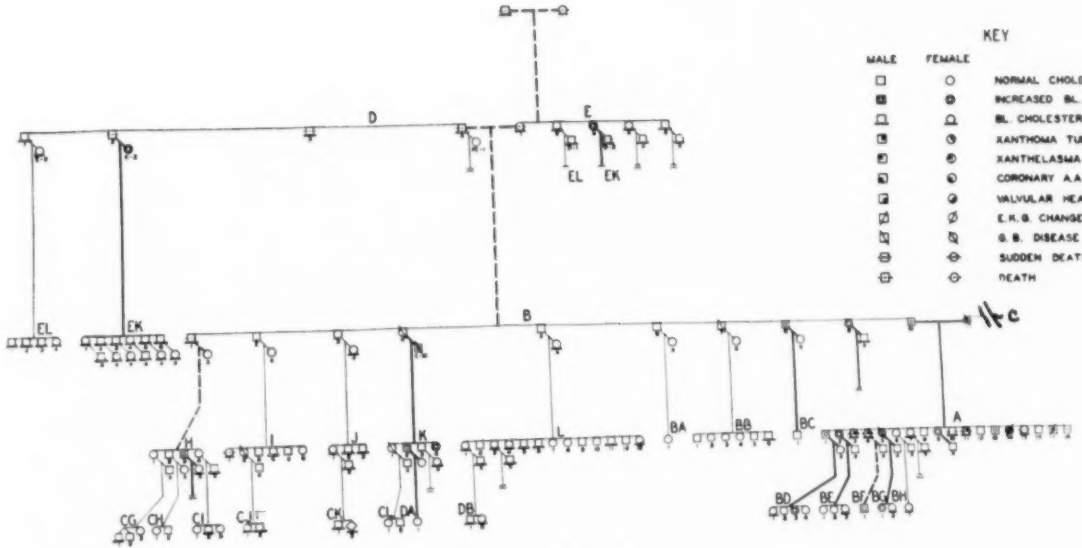
The Bloor[7] method for determining blood cholesterol was used in the initial survey because of the large number to be studied. The method was changed to the more accurate but time-consuming technique of Schoenheimer-Sperry,[8,9] when certain detailed metabolic studies were begun. The correlation of the blood cholesterol levels with the genetic pattern of transmission revealed a clear-cut distinction between normal levels and abnormal elevation of the blood cholesterol. We consider 280 milligrams per cent by the Bloor method and 210 milligrams per cent by the Schoenheimer-Sperry method abnormal elevations.

Many authors have pointed out that this condition is hereditary and many modes of transmission have been postulated. It is not difficult to understand these discrepancies when one realizes that it is rare to find reports in which two generations have been studied. Most of the reported families are small, or only a small number of the members was investigated. We were able to study four generations of large families and to examine nearly all living members of most sibships.

It can be seen from the family tree (Fig. 1) that whenever one parent had an elevated blood cholesterol, approximately one half of the children had an elevated blood cholesterol. When neither parent had an increased blood cholesterol, all of the children studied showed normal blood levels.

In the marriage of C-1 and B-10, both had an increased blood cholesterol. Of their eighteen children five had xanthoma tuberosum and/or tendinosum. Six had elevated blood cholesterol without skin lesions and four had normal blood cholesterol. Three are reported not to have had skin lesions, but their blood cholesterol level is not known.

In the union of A-4 (who had xanthoma tuberosum) and A-4x


KEY
MALE
FEMALE
NORMAL CHOLESTEROL
INCREASED BL. CHOLESTEROL
BL. CHOLESTEROL UNKNOWN
XANTHOMA TUBEROSUM
XANTHELASMA
CORONARY A.A. DISEASE
VALVULAR HEART DISEASE
E.K.G. CHANGES
G. B. DISEASE
SUDDEN DEATH
DEATH
D
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EL
EK
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BC
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Fig. 1 A

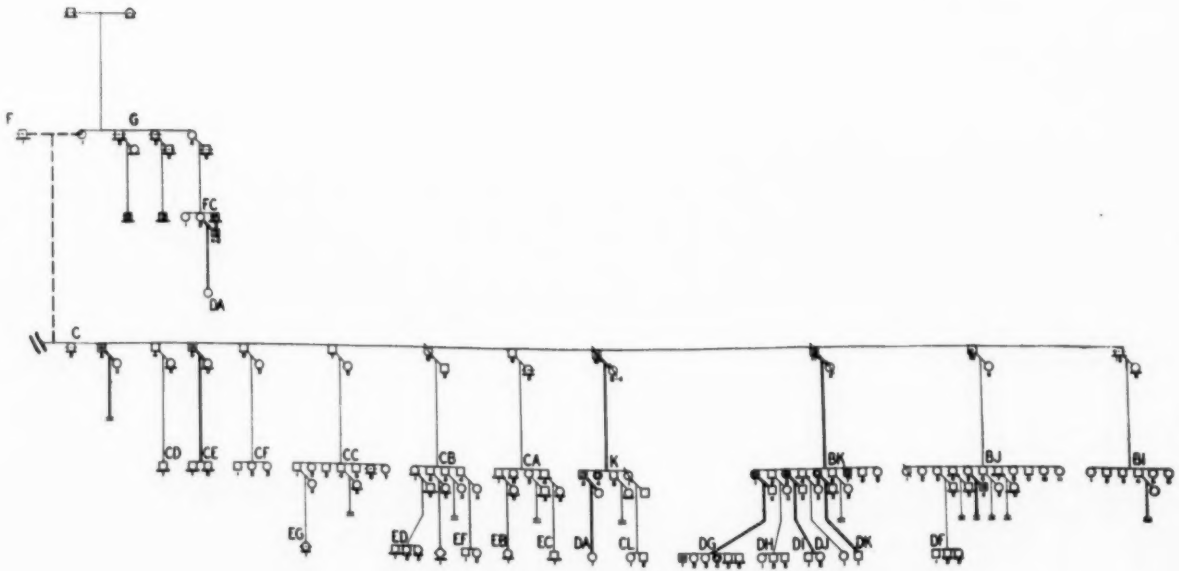


Fig. 1 B

Fig. 1—Due to the large number of individuals involved, it has been necessary to split this into two figures. The two parallel lines at the end of sibship B and sibship C represent the point where the pedigree was broken. The heavy lines show the transmission of essential familial hypercholesterolemia. The heavy broken lines show presumptive transmission of this trait (i.e.) either both parents were unknown or one was normal and the other unknown.

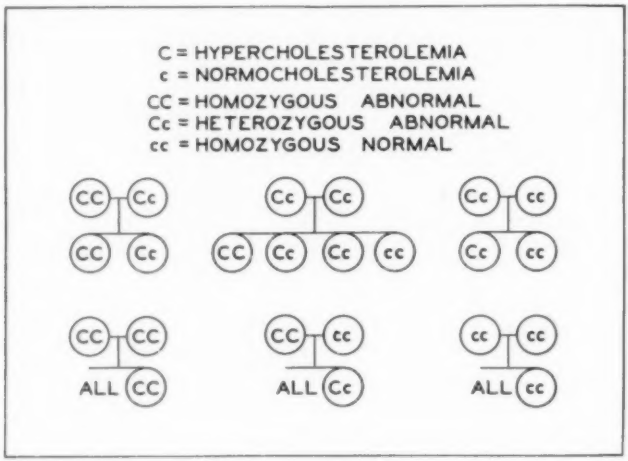


Fig. 2—Shows matings and predicted distribution of offspring.

(whose blood cholesterol was normal) the only child (BF-1) showed an increased blood cholesterol.

Of the five in sibship A who had xanthoma tuberosum and/or tendinosum, only two (A-14 and A-17) were studied by us; but Curtis, Wile, Eckstein and Duemling[10-12] reported observation on two others (A-3 and A-4), and though blood cholesterols were not reported, these cases were typical clinically and pathologically. The family physician and parents report that A-11 was likewise typical.

There is only one possible mating (homozygous abnormal x homozygous abnormal) that we have not observed to date. We feel, therefore, that our data are sufficiently complete and consistent to permit us to present a new theory concerning the mode of transmission (Fig. 2). We postulate:

1. That the metabolic disorder characterized by increased blood cholesterol which is designated by "C" (as against a normal blood cholesterol designated as 'c") is transmitted as a dominant.

2. Xanthoma tuberosum or tendinosum represents the homozygous abnormal.

3. A normal blood cholesterol represents the homozygous normal.

This type of inheritance is known as "incomplete" dominance be-

TABLE I—NUMBERS OF AFFECTED AND NORMAL CHILDREN AMONG OFFSPRING OF VARIOUS MATINGS

Matings	*Number of Matings*	*Elevated Blood Cholesterol*	*Normal Blood Cholesterol*	*Unexamined*
Heterozygote x Heterozygote	1	Observed 8	Observed 4	6
		Expected 9	Expected 3	
Heterozygote x Normal	9	Observed 11	Observed 13	5
		Expected 12	Expected 12	
Normal x Normal	11	Observed 0	Observed 41	7
		Expected 0	Expected 41	
Homozygous Abnormal x Normal	1	Observed 1	Observed 0	0
		Expected 1	Expected 0	

cause the severity of the condition is less in the heterozygote than in the homozygote

Table I shows the observed and predicted numbers of affected and normal children among offsprings of various matings in the kindred shown. In light of work done with other kindreds we feel that the penetrance is not 100 per cent. It was observed in one mating of a homozygous abnormal with a homozygous normal that one of three siblings had a normal blood cholesterol. It does seem, however, that the penetrance is very high.

It has been pointed out by many investigators that certain clinical and/or anatomical abnormalities seem to be associated with xanthomatous deposits in the skin.

The relative frequency of these complications in essential familial hypercholesterolemia is shown in Table II.

It will be noticed that xanthoma tuberosum and/or tendinosum occurred in two of the hypercholesterolemic group, and they have been discussed.

Xanthelasma was present in three cases of the group with increased cholesterol, and in one case in the group with normal blood cholesterol.

Arcus senilis to our surprise was present in only one case and here the cholesterol was normal. It should be pointed out, however, that a slit lamp was not used, as most of the examinations were done in the home.

TABLE II—RELATIVE FREQUENCY OF CLINICAL AND/OR ANATOMICAL ABNORMALITIES

	Hypercholesterolemia (30)		*Normocholesterolemia (129)*		*Statistical Significance* X^2
Xanthoma { Tuberosum / Tendinosum	(2)	6.6%	(0)		
Xanthelasma	(3)	10 %	(1)	0.8%	
Arcus Juvenalis/Senilis	(0)		(1)	0.8%	
Angina Pectoris	(1)	3.3%	(1)	0.8%	
Xanthomatous Valvular Heart Disease	(2)	6.6%	(0)		
Gall-Bladder Disease					
Clinical Story	(5)	17 %	(7)	5.4%	0.09
X-ray taken	(5)		(4)		
X-ray Positive	(2)	6.6%	(1)	0.8%	
Hepatomegaly	(5)	17 %	(3)	2.3%	0.01

Coronary artery disease as manifested by electrocardiographic changes and angina pectoris was found in one case of the hypercholesterolemic group. She had xanthoma tuberosum and had had typical symptoms of angina pectoris since the age of nine. There was one questionable case of angina in the group with normal cholesterol, his age being 59 years. No diagnosis of myocardial infarction was made by us, but three died a sudden death before this study was begun; and as they had xanthoma tuberosum, infarction secondary to coronary atheromatosis must be suspected. We have made detail studies of seven homozygous abnormal individuals in this and other kindred and have found five of them to have coronary artery disease.

Valvular heart disease was present in two cases. There was no history of rheumatic fever, scarlet fever, or chorea in either of these children. In view of the fact that several authors have reported xanthomatous deposits on the valves of the heart, we feel justified in assuming that the valvular defects are due to them.

We did not see any cases of biliary cirrhosis. Enlargement of the liver, however, was present in five cases of those with hypercholesterolemia and in three cases of those with normal blood cholesterol. None of the eight gave a history of jaundice or had increased urobilinogen in the urine; hepatomegaly was unexplained.

A clinical story suggestive of gall bladder disease was given in five instances in the hypercholesterolemic group; cholecystograms, however, were positive in only two. A similar story was obtained seven times in the normal group. Except for three, these were also x-rayed but only one had a positive cholecystogram.

Hypertension was found in two cases with increased cholesterol and in one case of normal cholesterol.

Splenomegaly was not found in this kindred.

The occurrence of secondary xanthoma in uncontrolled diabetes has long been known. It has been suggested by several authors that there is some relation between primary xanthoma and diabetes, or at least a decreased carbohydrate tolerance. There have been published, so-called pre-diabetic glucose tolerance tests on two members of this kindred.[10, 11] It must be pointed out, however, that these patients had been on a diet restricted both in carbohydrate and calories. It has been known for some time that a diabetic-like curve could be produced by starvation. Himswroth[13] has pointed out the necessity of properly preparing patients before doing a glucose tolerance test.

In view of the above, it was thought advisable to study the carbohydrate tolerance of this group.

Two patients with xanthoma tuberosum representing the homozygous abnormal; two patients with increased blood cholesterol and xanthelasma representing the heterozygous abnormal; and one patient with normal blood cholesterol representing the homozygous normal were placed on a standard glucose tolerance test preparatory diet for three days, and then five-hour tolerance tests were performed (Fig. 3). All of the five glucose tolerance tests were normal. There is then, no reason to expect people with essential familial hypercholesterolemia to show an altered tolerance to carbohydrate if they have been properly prepared for the test. Individuals with xanthoma tuberosum, therefore, do not belong in the group of potential diabetics.

During recent years it has been thought by many that the blood cholesterol level has some effect on the development of atheromatosis. It is thought by some that the amount of cholesterol in the diet is a factor not only in the production of atheromata, but also in determining the concentration of cholesterol in the blood.

Doubt has been expressed by others as to the importance of ingested cholesterol as a controlling factor of the blood level, and also as to its

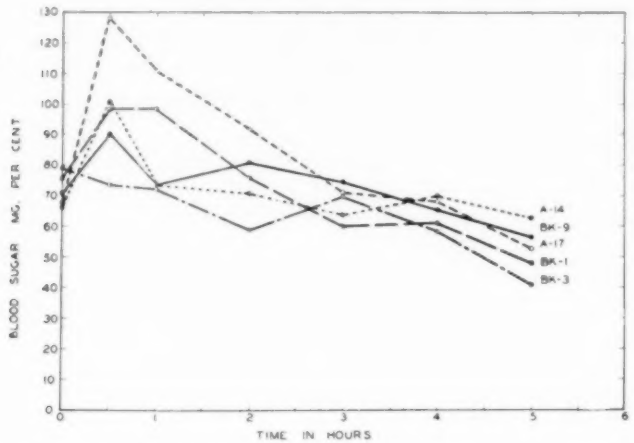


Fig. 3—Five hour glucose tolerance test showing normal utilization of carbohydrate.

etiological significance in atherosclerosis.

Many of the assumptions of those favoring a dietary factor in the production of atherosclerosis have been based on the fact that certain races of men have less atheromatosis than other races, and that they also ingest less cholesterol and animal fat. Any comparison of this type is difficult, and since so many other variables, both known and unknown, are present, conclusions may be fallacious.

Dietary habits are shaped by many factors, among which are: (A) economic considerations; (B) availability of foods; (C) personal likes and dislikes; (D) age in respect to freedom of choice; (E) dental repair; (F) religious and racial prejudices and taboos; and probably as important as any, (G) the dietary habits of the head of the house, be it male or female.

In this study as many as possible of these factors were kept constant. Most of the people studied lived in rural areas but approximately 20 per cent lived in cities. All had economic freedom of choice. Meals were planned, cooked, and served by one person, the housewife, in each of the several groups. The study was carried on long enough to rule out seasonal variation. The groups studied were told not to change their eating habits, and to record everything they ate.

We believe that comparisons of individuals studied in this way are inherently superior to broad generalizations where no effort is made to control or even enumerate known variables.

Families were chosen for observation in which there were people with essential familial hypercholesterolemia, as well as normal individuals. Usually one person, the mother, kept the records for the entire family and measured and recorded the types and quantities of food used by each individual at each meal. In every case a competent dietitian taught the recorder the technique of keeping food diaries. The records were kept for one or more weeks during the seven months of this study. The diaries were then analyzed, and the component parts of the diets were calculated from accepted food tables.[14]

It was found that the level of the total blood cholesterol was unrelated to the absolute amounts of carbohydrate, fat, protein, and cholesterol in the diet.

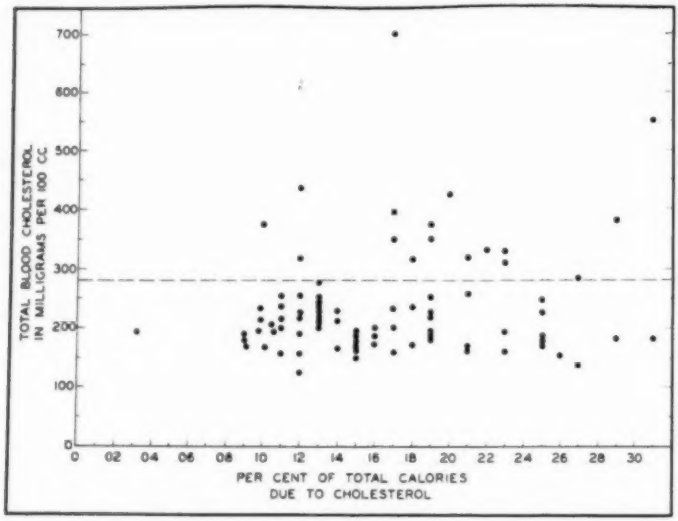
The ages of those studied varied from less than one year to fifty-nine years. It was concluded that a more significant comparison could be made if the per cent of the caloric intake resulting from each component was used as the variable, rather than the absolute amount. It was found that there was no relation between dietary composition and the total blood cholesterol level (Fig. 4).

Figure 5 shows the age distribution of the 159 individuals studied in detail in the large kinship of 282. The dietary study includes 83 or 52.2 per cent of that group. They were selected at random and usually before the values of their blood cholesterol were known. We feel justified, therefore, in using certain data collected during the larger study. Only two of the hypercholesterolemic are homozygous abnormal and they are less than twenty years of age.

Hypercholesterolemia, per se, appears to have no effect on life expectancy, when it is found in the heterozygous abnormal of essential familial hypercholesterolemia. In the homozygous abnormal, however, this is not the case. Atheromatosis may develop at an early age and is not uncommonly fatal.

We do not mean to imply that exogenous lipids have little or nothing to do with atheromatosis. On the other hand these data do give additional support to that school of thought.

After it was shown that large groups of individuals showed no relationship between their dietary composition and the level of their blood



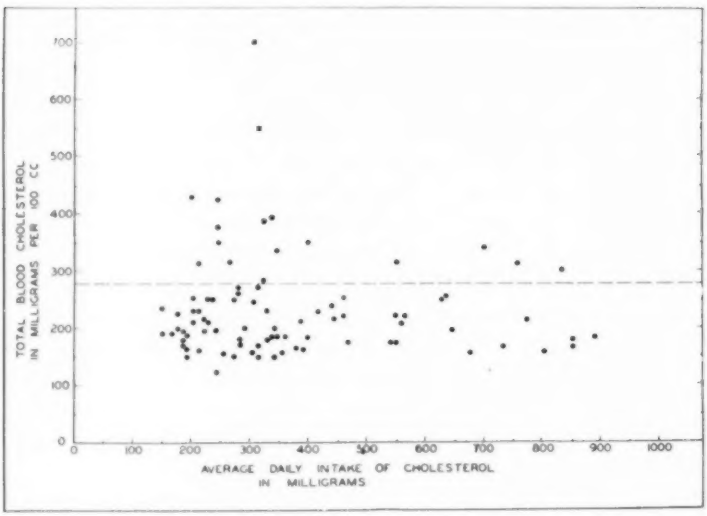


Fig. 4—This shows that there is no relation between cholesterol intake and the total blood cholesterol in the group studied. Similar graphs were obtained for carbohydrate, fat and protein. Total serum cholesterol levels are plotted as Bloor values.

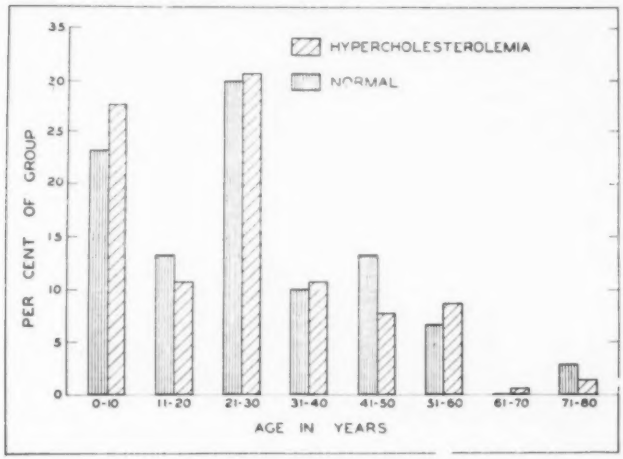


Fig. 5—Age incidence in the kindred represented in Fig. 1.

cholesterol, it was decided to try certain of these individuals on diets which varied the amount of cholesterol and see what effect this would have on the individual's blood cholesterol.[15] By giving only skimmed milk and substituting oleomargerine for butter and eliminating eggs from the diet, most of the cholesterol in an individual's diet can be eliminated. Figure 6 shows the longe range effect of reducing cholesterol in the diet to a minimum; it can be seen that in this subject there was no relation between the amount of cholesterol eaten and the height of the blood cholesterol.

An effort was made to reduce the blood cholesterol by the use of certain decholesterolizing substances. We could not demonstrate that either choline, lecithin or dried eggplant had any effect on the level of the blood cholesterol.[15,16] The knowledge that essential familial hypercholesterolemia is probably not rare has given rise to some speculation as to its frequency as well as to its effect on the clinical interpretation of total blood cholesterol values. Altogether, seven kinships other than the one shown in Figure 1, have been studied in detail by us, and others were not studied because of lack of time. It might give some idea as to the relative frequency of this disorder, to say that it has been found by

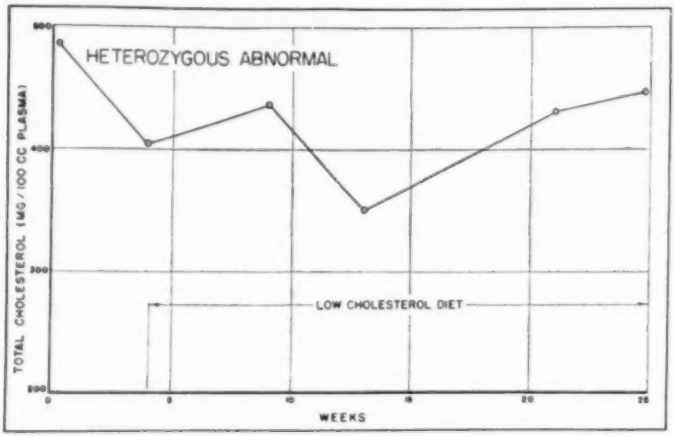


Fig. 6—It can be seen that while the blood cholesterol varied it showed no definite trend during the period of restricted cholesterol intake.

accident in three members of the clinical faculty of a medical school. Two of these cases were verified by genetic study.

An interesting case has been observed and reported[17] in which essential familial hypercholesterolemia was found in a patient suffering from hyperthyroidism.

The patient was placed on propylthyrouracil with fair clinical results. Two months later Lugol's solution was added and three weeks later a sub-total thyroidectomy was performed. Frequent determinations of the basal metabolic rate and blood cholesterol were made.

It was found that the blood cholesterol was increased throughout the period of observation and while it fluctuated, it was apparently unaffected by the basal metabolic rate.

This would seem to indicate that at times the blood cholesterol is not only of little value, as a diagnostic procedure in hyperthyroidism, but may even be misleading.

Because of the interest which arose as a result of the study of this case, it was decided to give individuals with essential familial hypercholesterolemia thyroid and see what effect this would have on their cholesterol level.[18] It was decided to maintain weight as constantly as possible during this period of exogenous thyroid administration. We

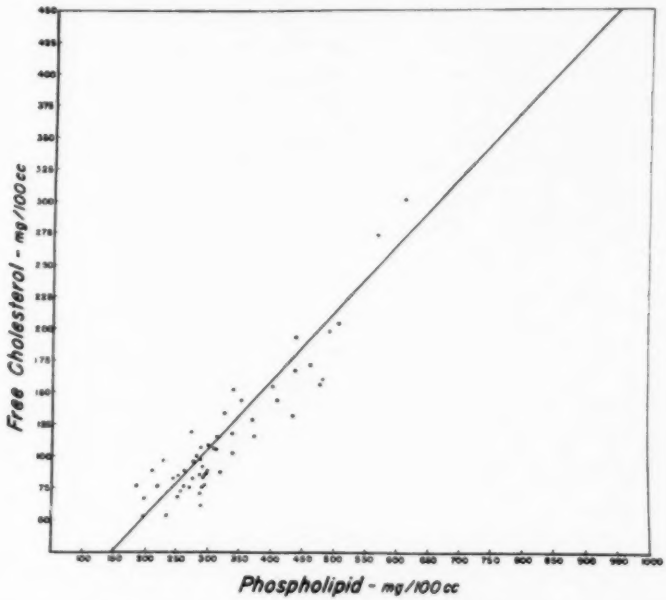


Fig. 7—This shows the distribution of individuals with essential familial hypercholesterolemia about the line representing the general relationship between phospholipid and free cholesterol.

were unable to determine any constant relationship between the basal metabolic rate and the level of the blood cholesterol.

Recently both Kellner[19] and Duff[20] have shown, in experimental animals, that one factor in the formation of atheromata is the relationship of the blood cholesterol to the other blood lipids. Because of the interesting observations of Kellner and Duff an attempt has been made to analyze all the data on lipid fractionations that my associates and myself have collected during the past three and a half years. We have, to date, found only one relationship that is constant in all of the cases we have examined. These cases not only include normal controls but individuals with essential familial hypercholesterolemia, diabetes, coronary disease, hypertension, hypothyroidism, hyperthyroidism and nephrosis. This material will be published in detail.[21]

We have found that there is an extremely constant relationship be-

tween free cholesterol and phospholipid in the plasma. Figure 7 shows the general relationship of some 240 separate examinations in the conditions mentioned above. All conditions studied bear a statistically significant relationship to this straight line. The Fischer "t" values vary from 3 to 13 which means that the probability that a group does not follow this general relationship is either one in one hundred or considerably less. It can be seen how those individuals with essential familial hypercholesterolemia follow the general trend. In fact, our highest correlation was obtained in this group.

There appears to be no demonstrable difference in the relationship between phospholipid and free cholesterol in individuals with essential familial hypercholesterolemia whether they are heterozygous abnormal or homozygous abnormal. While these individuals have elevated cholesterols they apparently do not differ as far as this relationship is concerned from normal individuals or individuals in whom the cholesterol is elevated secondary to some other condition.

Summary

1. It is felt that the term Essential Familial Hypercholesterolemia is preferable to others suggested in the past.

2. This condition is inherited as an incomplete dominant.

3. Xanthoma tuberosum represents the homozygous abnormal in this condition.

4. The upper limits of normal for blood cholesterol have been established by genetic pattern of transmission.

5. The relatively greater instances of certain pathological states in this condition as compared with normal individuals is pointed out.

6. No delay in utilization of carbohydrate could be demonstrated in this condition.

7. Dietary variations appeared to have no effect on the level of the blood cholesterol.

8. Various lipotrophic substances were utilized but it could not be demonstrated that they had any effect on the blood cholesterol level.

9. The hyperthyroid state does not seem to have any constant effect on the elevated blood cholesterol.

10. An exceedingly constant relationship between the free cholesterol and phospholipid has been demonstrated. This same relationship seems to exist in many conditions which affect the blood cholesterol level.

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ANTIHISTAMINES IN ALLERGIC AND NON-ALLERGIC DERMATOSES*

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At present it is assumed by most workers that the fundamental mechanism involved in allergic phenomena is the reaction occurring between antigen and antibody in the cellular tissue. As a result of this reaction, a histamine substance is released and the physiological activities of this agent account for the clinical symptoms of various dermatological allergies. The ability of the antihistamines to counteract these effects and in some instances to prevent them from manifesting themselves has led to their investigation and employment by the dermatologist.

Ephedrine and other sympathomimetic drugs are histamine antagonists which neutralize the effect of histamine by producing an opposing action. That is, the latter produces bronchial constriction while the former relaxes the bronchial muscles. Histamine decreases blood pressure while ephedrine raises it. Antihistamines are not antagonists like ephedrine. Theoretically, they have no physiological action as they do not raise or lower the blood pressure and they do not contract or relax bronchial musculature. However, we know that this belief is not entirely true by virtue of the imposing list of toxic manifestations which they produce on patients. Their function is one of a blocking agent. Therefore, they do not prevent the release of histamine from the cell, nor do they prevent its action once it has taken place. However, they are capable of preventing the histamine substance from combining with the effector cells in such a manner as to produce its classical effects. The historical background and chemistry of these compounds have been presented in a previous publication.[1]

The antihistamines have been investigated extensively as to their ability to counteract histamine effects in the animal and in the human. From the dermatological viewpoint, it is interesting to review some of

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the clinical and experimental observations of the behavior of these drugs. The fundamental work on the human was performed with the earlier drugs like pyribenzamine and benadryl. It can be assumed that all of the present proprietary drugs that have been accepted by the Council on Pharmacy, will show the same experimental results with only minor quantitative differences.

Dermographism: Friedlaender and Feinberg,[2] found that small oral doses given 1 to 2 hours prior to skin testing will entirely abolish dermographism.

Urticarial wheals: Many workers have proven that small oral doses of antihistamines will reduce intradermal histamine wheals. Similarly the wheals produced by specific allergens are likewise reduced by oral ingestion of 50 to 100 mgm. of antihistamines taken about 45 minutes before performance of the skin testing.

Passive transfer: Antihistamines will decrease the size of the reaction in passive transfer sites when the drug is given approximately one hour before the local sites are injected intradermally with the specific allergen used.

Effect of local application: When ragweed extracts are combined with antihistamines, the latter are capable of inhibiting both the flare and wheal of the reaction upon a ragweed sensitive patient who is being scratch tested. Histamine reactions produced on the skin by local scratch testing or local injection of such agents as codeine, morphine and atropine are similarly diminished by antihistamines. Topical antihistamines applied to the scratched sites significantly reduce the size of the wheal that is normally produced by these drugs. This gives further credence to the theory of the H-Substance of Lewis occurring as a common mechanism involved in all such reactions.[3]

Anesthesia: An anesthetic ability is inherent in at least some of the antihistamine preparations. Early observers noted that accidental contact of a solution of benadryl on mucous membranes of the mouth produced numbness for a considerable period of time. A 1-5000 solution of benadryl injected intradermally will give complete anesthesia.[1]

Actinic inhibitory effect: Experimentation has shown that the antihistamines are excellent as sunburn preventives. It has been demonstrated that a 5 per cent solution of pyribenzamine absorbs or filters out those wave lengths of the ultraviolet spectrum which are known to cause erythema (2800 to 3100 A Units and to a lesser degree 2537 A

Units).[4, 5a] However, this is not thought to be due to the antihistaminic action of this drug. It is attributed to the ability of the pyribenzamine to filter or absorb these particular wavelengths of the spectrum.

These agents also appear capable of affecting X-ray irradiation of the skin. Mains[5b] in treating 100 cases with high voltage X-ray, found that there was less reaction and a marked increase in skin tolerance to the irradiation when he used either local or oral antihistamines or combined both types of medication. He employed benadryl and pyribenzamine in these experiments.

Anticholinergic effect: All antihistamine drugs appear to possess anticholinergic as well as antihistaminic activity. That is, they are capable of counteracting the effects of acetylcholine which is one of the components of the allergic mechanism, at least in certain reactions. It is further believed by some to be a factor in the pruritic mechanism. This important factor of the antihistamines may account for their successful role as an antipruritic in some of the non-allergic dermatoses. When acetylcholine is injected into the skin, benadryl has been shown to be fifty times as effective an antagonist as papaverine, an effective acetylcholine antagonist.

Central nervous system: Stimulative and sedative effects of antihistamines are well known side reactions that are even taken advantage of in management of the patient in some instances.

Churchill and Gammon[6] demonstrated the effect of these agents on the central nervous system. They were able to produce excitation of the cerebal cortex in epileptics sufficient to bring about convulsive seizure. Benadryl has a sedative effect while pyribenzamine seems to have the opposite reaction. They postulated that this effect arose from the stimulation of the reticular system of the thalamus.

This characteristic of certain of these agents may account for their effectiveness in controlling pruritus where it may be of central origin.

Inhibition of hyaluronidase: Hyaluronidase, an enzyme, is thought to enhance the size and intensity of allergic skin inflammations of the epidermal type. Mayer and Krell[7] have shown that antihistamines are capable of decreasing this effect of hyaluronidase. This further suggests that hyaluronidase plays some part in the mechanism of production of epidermal sensitizations.

Effect on hematopoietic system: Prolonged use of these drugs in animal and human experimentation has shown relative absence of any

toxic effect on the liver or on the blood cellular constituents. However, these drugs are not entirely free of such an effect. Cahan, Meilman, and Jacobson[8] recently reported the development of an agranulocytosis in a patient treated with pyribenzamine for 5½ weeks for contact dermatitis. Several other cases of granulocytopenia[9, 10] have been reported following administration of antihistamines for other conditions. The reaction has developed within a three to eight week period of time. Drugs having the benzene ring have been notable for this type of reaction.

Sometime ago, the author reported the development of an agranulocytopenia following the use of quinine in a case of malaria therapy for syphilis.[10] The presence of the ring formation in the quinine compound was mentioned as a usual characteristic of agents capable of producing this type of blood dyscrasia.

Drake[11] suggests that reactions may not have been experienced after the extensive use of benadryl because its benzene rings are attached through a carbon rather than a nitrogen atom. Thus far, reports would indicate that preparations having a nitrogen linkage, are capable of producing agranulocytosis. In view of these observations, it might be advisable to use antihistamines having either a carbon or oxygen linkage when these drugs are to be administered over prolonged periods of time. Such preparations include Trimeton, Thephorin and Decapryn. Benadryl does not have a nitrogen linkage but its high incidence of side effects must be considered.

Results of Oral and Topical Therapy

At the New York Hospital and in private practice we have observed the effect of both oral and local antihistamine administration on a wide variety of allergic, as well as non-allergic dermatoses; eight available antihistamine drugs were orally administered; seven of these were employed in topical applications. In all, 666 patients were treated either by oral or local medication or by both. In most instances patients were treated with several of the drugs in order to compare the results of effectiveness of each drug in the same condition on the same patient. Therefore, there was a total of 1439 drug trials. The oral preparations were administered in 25 to 50 mg. doses 3 or 4 times daily. The local ointments contained 2 per cent concentrations of the drug. In a few instances a 5 per cent ointment was employed. As a control in the series

TABLE I—RESULTS IN ORAL MEDICATION

Disease	*No. Drug Trials Total 565*	*Per Cent Relieved* **	*Per Cent* Relieved*
Urticaria	180	80	—
Localized Neurodermatitis	47	64	66
Atopic Eczema	142	58	62
Contact Dermatitis	38	47	47
Pruritis Ani, Vulvae et Scroti	20	25	67
Miscellaneous Dermatoses	138	47	37

* Per cent relieved with additional local medication.
** Patients in which drugs were 40 to 100 per cent effective.

placed on local preparations, a number of the patients were tried on an ointment containing ½ per cent menthol and ½ per cent phenol. Others were given a placebo using an aresol emulsion base for treatment. For convenience, the cases are divided into 6 groups and referred to in this fashion. The estimation of the response to treatment is given in accordance with the recommendation of the American Academy of Allergy. Fair indicating 0 to 40 per cent; good 40 to 60 per cent and excellent 60 to 100 per cent effectiveness. The use of a large number of the currently commercially available drugs afforded an opportunity of estimating the value of the antihistamines in general as well as any individual differences of their efficiency.

Urticaria: The oral antihistamines are undoubtedly superior to any other therapy in control of urticaria. All types, especially the acute forms, gave excellent response to most of the drugs that were investigated; 80 per cent of the cases with this type of dermatological manifestation experienced good results from antihistamine therapy. Trimeton and Neoantergan gave evidence of the best results and Decapryn and Tagathen were consistently effective. Histadyl showed up well but there were only 2 drug trials.

Localized neurodermatitis: Oral antihistamines were found to give relief in only 64 per cent of these cases; the major effectiveness, of course, being the reduction or complete elimination of the pruritus, a main component of this skin entity. With topical medication the results were excellent as 82 per cent of the patients showed definite relief of

TABLE II—INCIDENCE OF SIDE REACTIONS
(ORAL MEDICATION)

Drug	*Number of drug trials*	*Number of side reactions*	*Per cent side reactions*
Thephorin	258 (237)	64 (42)	25 (18)
Neoantergan	96	19	20
Tagathen	64 (40)	17 (7)	22 (18)
Trimeton	144 (120)	34 (23)	24 (19)
Benadryl	46	20	43
Pyribenzamine	105	20	19
Decapryn	51	9	18
Histadyl	30	7	23
	794 (725) total	190 (147) total	24 (20) average per cent

Expressed in percentage Figures in parenthesis on 25 mgm.

pruritus. Of course, in this type of skin involvement, if one can obtain relief from the pruritus, resolution of the lesions will ensue. These never ointments were superior to the old type antipruritics as shown by the fact that only 53 per cent of cases receiving the menthol-phenol preparation experienced relief and the base alone gave no appreciable effect.

Disseminated neurodermatitis (atopic eczema): In the generalized type of atopic dermatitis these drugs are of definite help. The oral preparations gave relief in 58 per cent of the patients treated. Thephorin, Trimeton and Decapryn gave somewhat superior results while Benadryl did very poorly. The results with local therapy in this group, however, were much more favorable. This has also been the conclusion of other workers; 74 per cent of patients receiving local antihistamines were given good relief. This is further substantiated by the fact that only 25 per cent of this group of patients experienced relief with the menthol-phenol preparation and none were aided by the application of the placebo base. Thephorin ointment gave excellent benefit in atopic eczema. The antihistamines afford a new and much more satisfactory approach to this dermatological complex than any that we have previously had. The effectiveness of these agents in this entity would add weight to the argument favoring its allergic mechanism in many instances.

TABLE III—COMPARISON OF EFFECTIVENESS OF TOPICAL THERAPY IN ALL GROUPS TREATED

Drug	*No. drug treats.*	*Per cent relieved*	*Per cent reaction*
Thephorin	194	83	4
Histadyl	66	79	3.5
Trimeton	94	78	3
Thenylene	63	73	7
Pyribenzamine	143	66	6
Benadryl	46	65	4
Decapryn	38	45	5
Total	644		

Contact dermatitis: Only 47 per cent of the cases of contact dermatitis received a good measure of relief from oral administration of these drugs. There was no effect upon the lesions, only upon the pruritus. With the use of the topical application 64 per cent showed good results. However, these cases were carefully selected. They are no indication of the results to be expected from local use of these agents if acute and generalized types of contact dermatitis are chosen for treatment. In such a situation, the incidence of reactions would far outweigh the usefulness of the local drug.

Pruritus vulvae, ani, scroti: Orally, the antihistamines have proved of little value in the treatment of this type of dermatosis. Only 25 per cent of these patients treated with oral medication were afforded relief. While with local application, the results were second only to the efficacy experienced with the use of oral antihistamines in urticaria; 79 per cent of these patients received good relief. This convincing evidence would indicate that local antihistamines are an excellent form of therapy in this type of pruritus, always a difficult therapeutic problem. Of course, the treatment is not permanent, although in some cases prolonged intervals of freedom from symptoms is obtained. Local placebo treatment gave no relief in these cases. Only 28 per cent experienced relief from the menthol-phenol preparation. Thephorin, Benadryl and Thenylene gave excellent benefit. Pyribenzamine did not seem as effective.

Miscellaneous pruritides: In some instances a patient having a mis-

TABLE IV—COMPARISON OF RESULTS IN ORAL AND LOCAL THERAPY (PER CENT RECEIVING RELIEF)*

	Topical Therapy	*Oral Therapy*	*Oral Antihistamines combined with other Rx*	*Menthol and Phenol Ointment*	*Controls*
Urticaria		80			
Localized Neurodermatitis	82	64	66	53	11
Atopic Eczema	74	58	62	25	0
Contact Dermatitis	64	47	38	20	16
Pruritus Ani, Vulvae, Scroti	79	25	67	28	0
Miscellaneous Dermatoses	38	47	37	20	10

* Patients in whom drugs were 40 to 100 per cent effective.

cellaneous dermatosis with pruritus as a prominent presenting symptom which will respond to no other form of treatment will experience dramatic relief upon administration of oral antihistamines. In this group were placed many varied diagnoses, some having a presumption of an allergic mechanism, as erythema multiformi or drug eruptions, others with pruritus as a symptom of their disease as in mycosis fungoides, lichen planus and psoriasis. In the former group it was felt that the antihistamines might affect the fundamental mechanism producing the disease, in the latter group the mechanism resulting in the pruritic manifestation of the disease. Results in these cases which included some 24 separate entities were equivocal. An average of 38 per cent were helped by oral administration and 47 per cent by local application of the antihistamines. Tagathen, Neoantergan and Trimeton gave the best results of the drugs employed by the oral route. Locally, Thephorin and Histadyl gave good results while Benadryl and Pyribenzamine were not as effective. A few chronic dermatoses, particularly scleroderma, were treated over a period of three to five months without noticeable effect on the disease. Repeated blood counts and urine analyses on these cases showed no evidence of toxic effects due to the drugs.

Reactions: The antihistamine drugs are not free from reactions either by the oral route or by local application. In the former, 20 per cent showed side reactions, none markedly severe. These have been reported in detail in another publication.[1] With local antihistamines there was an average incidence of reaction of 4.5 per cent of carefully selected

cases. The local reactions took the form of a dermatitis of the contact eczema type of sensitivity with actual allergic reaction developing or as a primary irritation. When a patient experienced these reactions either from local medication or by oral ingestion, he was usually changed to another agent or agents which eventuated in securing one in which the side effects were eliminated or at least sufficiently decreased to allow continuation of treatment.

The local agents, if used in actively eczematized conditions or in an extensive generalized involvement, will result in untoward effects in 12 to 20 per cent of the cases to be treated. They are not the drugs of choice in the average contact dermatitis such as an acute ivy dermatitis. Other types of dermatological therapy give superior results. Even in pruritus ani where their effect is excellent, they will produce a dermatitis venanata if applied to an acutely eczematized membrane. During the acute stage these lesions must be managed with a proper dermatological regime before treatment with local antihistamines is instituted. As has been evidenced above, these drugs are efficacious in many dermatological entities. They will prove more helpful if additional forms of dermatological therapy are employed as indicated by the particular condition.

Parenteral Administration: The parenteral use of these drugs is often beneficial where oral and local medication fail or where for some reason they cannot be employed. I have used intravenous antihistamine with success. In one case of a generalized erythema due to a penicillin sensitivity where oral antihistamine had given no relief there was prompt response within forty-eight hours. Again in a far advanced cancer case with an erythematous severely pruritic reaction to a barbiturate in which oral administration was impossible and local medication not indicated because of the generalized reaction, 10 to 20 mg given twice at four hour intervals gave excellent relief to the pruritus and was followed by resolution within seventy-two hours of the major portion of the dermatitis. The intravenous drug is still in the experimental stage. Muscular spasticity and fall in the blood pressure which sometimes follows, is a serious detriment to its extensive use. Further work must be performed before this form of therapy can assume general clinical adoption. When given by the subcutaneous or intramuscular route some of these drugs are capable of producing necrosis locally and are very painful upon injection.

Comment

Recognition of the effectiveness of the antihistamines on the reduction of edema and pruritus in controlling the clinical manifestations of allergic dermatoses, particularly urticaria, led to their general application in the treatment of pruritides by the dermatologist. The internist early employed these drugs successfully in the relief of pruritus associated with icterus and diabetes. The ability of the antihistamines to block the action of histamine, logically accounts for their effectiveness in controlling the symptoms of certain allergic dermatoses as well as altering the clinical course of other cutaneous diseases presumably having an allergic mechanism. But why should these agents be helpful in allaying pruritic manifestations of some dermatoses entirely unrelated to allergies? Why, for instance, should a patient with a severely pruritic psoriasis or itching lichen planus or a most uncomfortable Duhring's disease or leukemia receive some measure of relief from these drugs? That these drugs are capable of such results has been confirmed now by too many recognized workers in the fields of allergy, internal medicine, and dermatology, to attribute it to any psychic effect. It would seem that in pruritus, resulting from some pathologic or degenerative metabolic process, as in leukemia or jaundice, that there are products produced other than histamine which excite the itch mechanism and which the antihistamines are capable of interfering with. The itching in these diseases is definitely not that of a histamine effect as histamine always produces actual tissue change such as the urticarial wheal, while in some of these conditions there is itching without demonstrable tissue alteration.[12]

Rothman,[13] in discussing the physiology of the itching mechanism, has stated that in the itching of pregnancy, diabetes, liver disease and that of the hematopoetic system there must be some substance other than histamine which is the mediator, as no gross or microscopic changes are seen. Histamine in concentration sufficient to evoke itching causes visible skin change. Metabolic products of these pathologic conditions evidently act directly on the nerve ending or they produce a chemical mediator of another substance.

One substance capable of producing pruritus without concomitant tissue change is acetylcholine. It has been considered by others to be one of the factors responsible in the production of itching.[14] It is also involved in the production of intrinsic asthma and certain emotional

allergies through chemical nerve mediation of the autonomic system, particularly the parasympathetic nerves.

Hopkins, Kesten and Hazel[14] and Grant, Pearson and Comeau[15] reproduced urticarial attacks in patients suffering from emotional and physical urticaria by injection of an agent Carbochol (Doryl [Carbaminoylcholine Chloride]) which has the same physiological action as acetylcholine. More recently Nomland,[16] using mecholyl, an acetylcholine derivative, reproduced symptoms of itching in 4 patients having generalized itching without manifesting urticaria as a result of physical and emotional influence. Urbach[17] quotes several French authors (Villaret, Vallery-Radot and others) as having the opinion that the symptoms of allergy may depend upon an excess of acetylcholine or some disturbance in its normal breakdown by choline esterase. There is likelihood that more than one substance is concerned in the allergic mechanisms which are released from the tissue reactions and affect the autonomic nerve and the effector organs. Some of the clinical manifestations of allergy have been considered possibly a response of the organism to a substance like acetylcholine in normal tissue constituents. The theory of chemical mediation of the nerves is now generally accepted. When the sympathetic nervous system is stimulated, adrenergic substances (epinephrine-sympathin) are secreted by the cells in which the sympathetic nerves have their ending. Cholinergic substance (acetylcholine) is released when the parasympathetic fibers (vagus) are stimulated. The terms cholinergia and adrenergia are now in general use signifying imbalance of the autonomic nerve activtiy. Patients with dermatitis, urticaria, angioneurotic edema, asthma and vasomotor rhinitis often demonstrate other features of cholinergia such as excessive sweating, salivation, hyperacidity, indigestion, spastic colon, dermographism and pruritus. Adrenergic drugs (ephedrine) give these patients temporary relief of their symptoms.

Rothman and Coon[18] presented experimental evidence suggesting the presence of acetylcholine in fluid from lesions of allergic eczema and dermatitis herpetiformis. These workers have also demonstrated that acetylcholine is liberated in histamine wheals and is present in some inflammatory skin lesions. Wybauw[19] likewise has demonstrated that the axon reflexes, running through the sensory nerves responsible for the flare about the histamine wheal, produce acetylcholine at the terminals of these sensory nerves.

Mayer[7] has stated that all antihistamines have anticholinergic activity and thus counteract acetylcholine effects, there being only quantitative differences in the relationship of these activities in one substance. Thus there has accumulated evidence that acetylcholine or similar substance, plays some part in the production of these mechanisms upon which the antiacetylcholine action of antihistamine may have a definite influence.

Another paradox which is difficult to explain, is the excellent results experienced with antihistaminic drugs in urticaria, and their failure in many other types of allergic dermatoses. The fact that only about 1 in 5 urticarial eruptions are on an allergic basis, adds confusion to consideration of the action of these drugs. The superiority in some instances of topical antihistamines over the use of the drugs orally in certain cases of atopic eczema is also puzzling.

Gilman[20] has offered a possible solution to this question from interpretation of the pharmacological action of these drugs. First, the fact must be kept in mind that antihistamines do not prevent the release of histamine but rather prevent its gaining access to the receptor mechanism in the cell, and there exerting its characteristic effects. A laboratory animal can be protected by antihistamines against hundreds of lethal doses of histamine injected intravenously. On the other hand, it is difficult to protect a sensitized animal with antihistamines against a single lethal dose of a sensitizing antigen. In an antigen-antibody reaction where the site of release of the histamine is intracellular, there is little opportunity for a drug to block the effect of such a substance. In other instances where histamine substances come to the cell by the way of circulation, an agent such as antihistamine may be highly effective in blocking its effects. It seems reasonable then to suppose that where the reaction to histamine depends upon the release and subsequent diffusion of histamine, there can be an effective block established by antihistamines, while reactions resulting from a release of histamine directly in the effector cells cannot be effectively blocked. Perhaps this may afford an explanation of the actual effect of the antihistamines in certain urticarias where there might be present a histamine or histamine-like agent in the circulation and where reaction takes place in the blood vessels of the cutis. Here the condition results from extravasation of fluid causing localized edema which is directly responsive to antihistamine therapy. Again, topical applications may have superior benefit

in such conditons as atopic eczema, where the local antihistamine effect is not sufficiently influenced by oral administration. The antihyaluronidase effect of the antihistamines may also account further for the effectiveness of the antihistamines in certain dermatoses, such as certain cases of contact dermatitis.

This brief consideration of the possible factors involved in these allergic dermatoses and itching of non-allergic origin may make more plausible the efficiency of the antihistamines in the treatment of the dermatoses in the series observed.

Conclusion

Antihistaminic therapy does not supplant other forms of therapy or the usual routine dermatologic care of patients. This group of drugs has proven successful in a large enough percentage of cases and has demonstrated such dramatic relief of symptoms in others, that their use is warranted in many instances. Employed as an additional drug in our therapeutic attack on allergic dermatoses and pruritic symptoms of some non-allergic dermatoses, they are a welcome and much superior product in many respects to older remedies. However, the antihistamines should not be employed as a substitute for correct diagnoses nor a short cut for thorough investigation. Locally, they are contraindicated in generalized or acute dermatoses. Their prolonged use without observation is to be condemned. The antihistamines are not curative nor do they offer an easy road to the determination of a cause, although they may help to make the path an easier one for both the patient and the physician to pursue.

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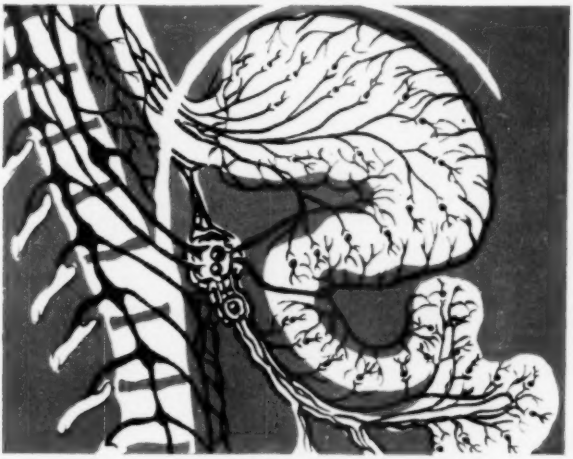

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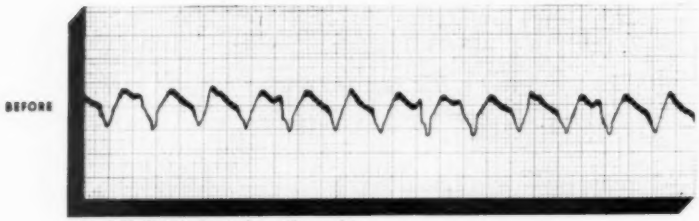
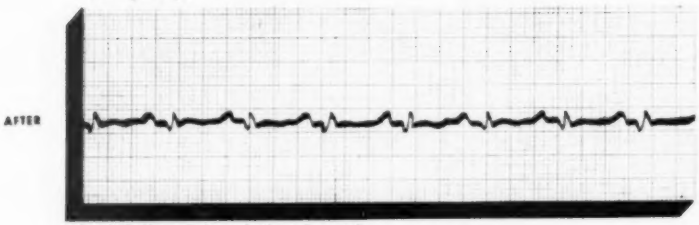


Lead II. Ventricular tachycardia persisting after six days of oral quinidine therapy (8 Gm. per day).



Lead II. Normal sinus rhythm after oral Pronestyl therapy.

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In conscious patients, for the treatment of ventricular arrhythmias.

During anesthesia, to correct cardiac arrhythmias.

What are its advantages in ventricular arrhythmias?

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Pronestyl has been found effective in some patients who failed to respond to quinidine.

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Intravenously, Pronestyl is much less toxic than procaine. In the recommended intravenous dosage, Pronestyl does not cause the central nervous system stimulation typical of procaine in conscious patients.

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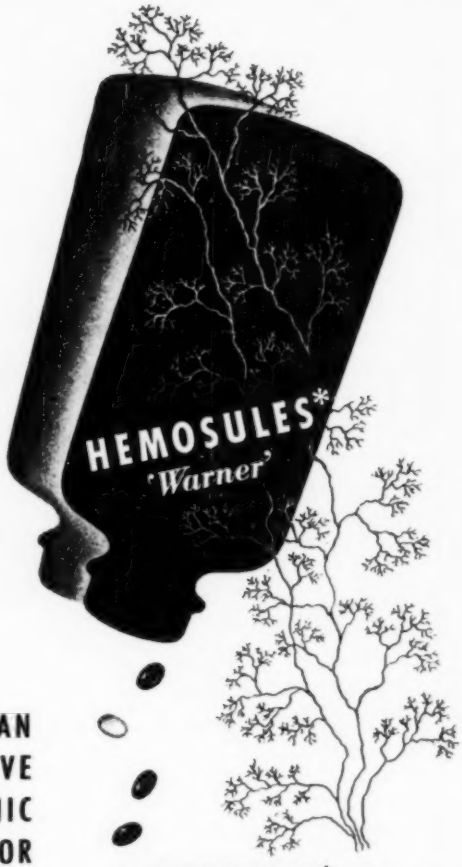

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Ley, H. L., Jr.; Smadel, J. E., and Crocker, T.: Proc. Soc. Exper. Biol. & Med. *68*:9, 1948

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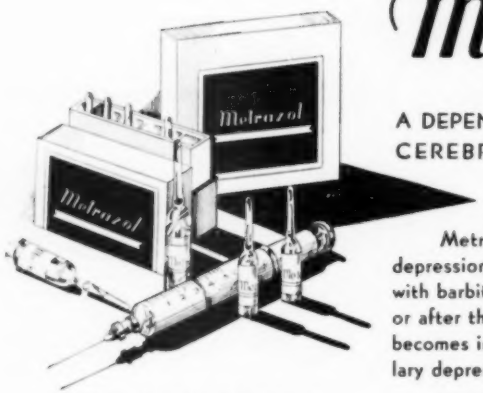

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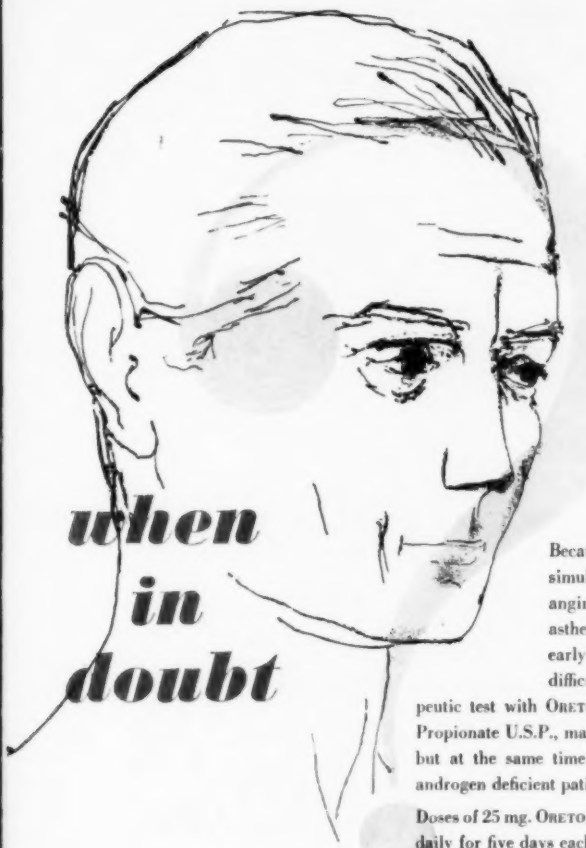

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1. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Industrial Med. & Surg. 18:512, 1949.

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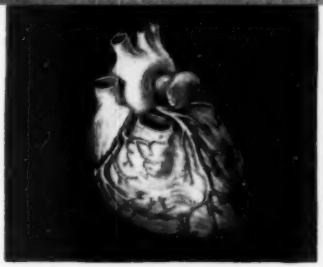

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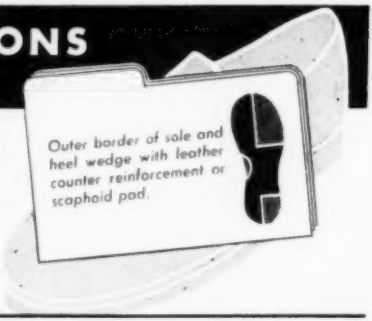

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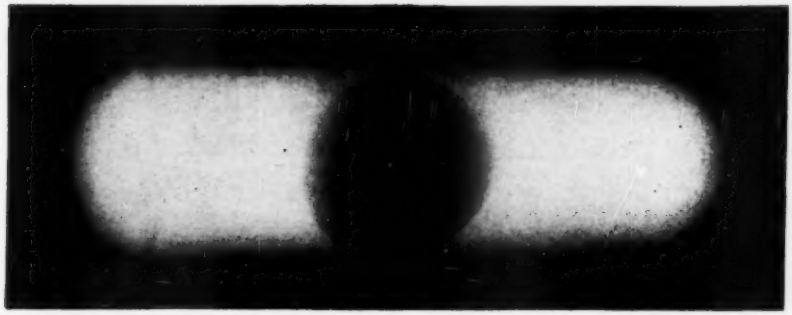

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History: Pyelonephritis, 1½ years' duration following ureterocutaneous implants (mixed infection: P. vulgaris, E. coli, Staph. albus, enterococci); previous therapy with all available antibiotics and chemotherapeutic agents without response.
Therapy: Terramycin, 2 Gm. daily for 5 days; orally in divided doses q. 6 h.
Result: Urine culture negative except for P. vulgaris by 2nd day of treatment. Response described as "good".
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1. King, E. Q.; Lewis, C. N.; Welch, H.; Clark, E. A., Jr.; Johnson, J. B.; Lyons, J. B.; Scott, R. B., and Cornely, P. B.: J. A. M. A. 143:1 (May 6) 1950.
2. Herrell, W. E.; Heilman, F. E.; Wellman, W. E., and Bartholomew, L. A.: Proc. Staff Meet. Mayo Clin. 25:183 (Apr. 12) 1950
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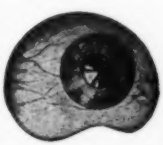

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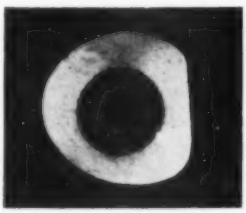

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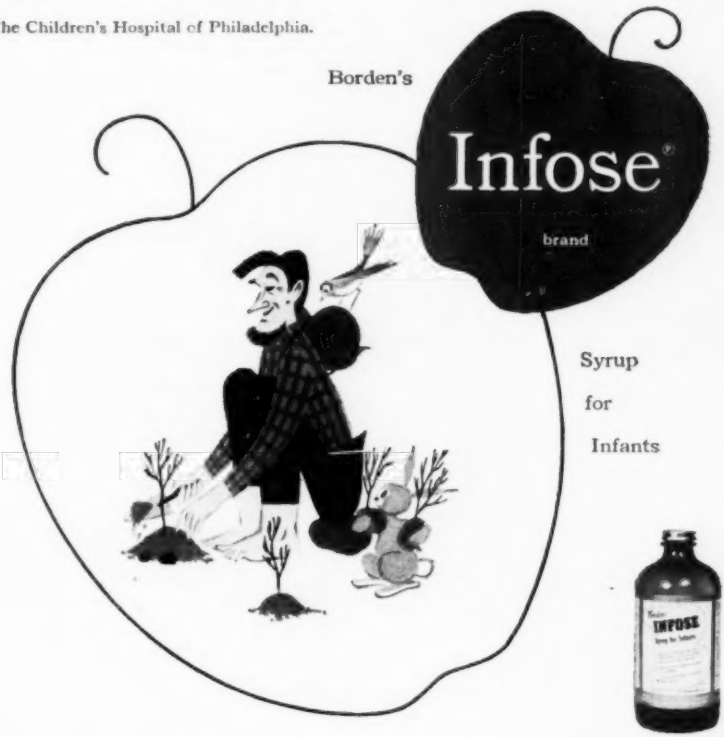

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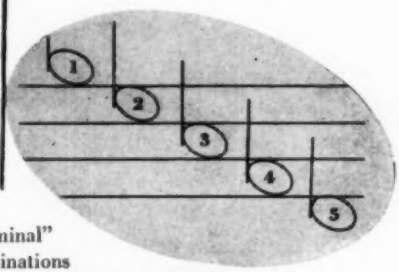

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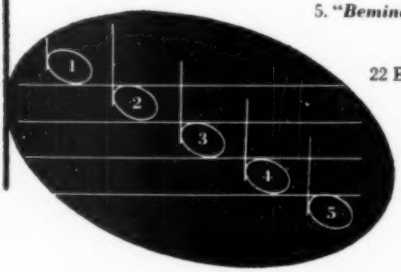

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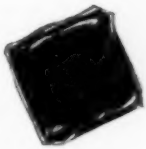

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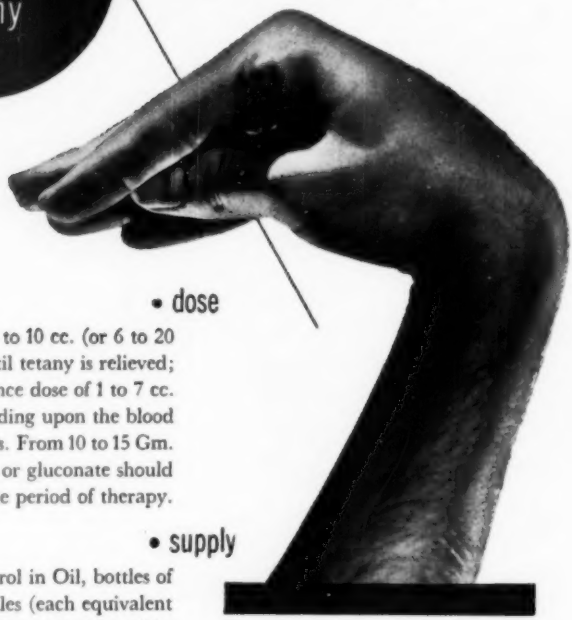

• dose

Orally 3 to 10 cc. (or 6 to 20 capsules) daily until tetany is relieved; weekly maintenance dose of 1 to 7 cc. or 2 to 14 capsules depending upon the blood and urine calcium levels. From 10 to 15 Gm. calcium lactate or gluconate should be given daily through the period of therapy.

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The relation between the amount and the physical state of circulating cholesterol and its deposition in the vascular intima is emphasized by recent investigations.

Morrison and his associates have shown that (1) coronary occlusion is often associated with hypercholesterolemia; (2) the coronary arteries of patients who died of coronary occlusion contained four times as much cholesterol as the coronary arteries of a control group; (3) lipotropic therapy reduced the blood cholesterol and prolonged the lives of patients who had had an occlusion.

Gofman and his coworkers have demonstrated that deposition of cholesterol in the blood vessels is always associated with the presence of circulating cholesterol containing macromolecules.

For the prevention and treatment of Atherosclerosis the Rawl Chemical Company presents METHEPONEX CAPSULES, the first and only *complete lipotropic* preparation containing *whole liver* and all the factors of the vitamin B complex.

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REFERENCES

Morrison et al: Am. J. Med. Sci., 216:23, July 1948; Am. Heart J., 39:31, Jan. 1950; Circulation, 2:120, July-Aug. 1950.

Gofman et al: Science, 111:2877, Feb. 1950; Circulation, 2:161, Aug. 1950.

Literature and Samples on request

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